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OFFICIAL JOURNAL OF THE CALIFORNIA MEDICAL ASSOCIATION

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Volume 84

JUNE 1956

Number 6

Influenza: Theme and Variations

C. H. ANDREWES, M.D., F.R.C.P., F.R.S., London

THE THEME OF THIS PRESENTATION is the influenza virus and its antigenic structure. Its structure varies in a remarkable way and the variations played upon the theme may be of vital importance to understanding of the disease and to success in controlling it.

All physicians know influenza and how hard it may be to define clinically. There are fever, aches of head, of back, of limbs, malaise and varying degrees of involvement of the upper respiratory tract. For general practitioners "flu" is a convenient name for infections of this sort. Physicians generally are also aware that periodically, at least in Europe, roughly every two years, influenza is likely to attack very large numbers of people at once and to cause much disturbance to our daily life. When this happens, it is nearly always influenza virus *A* that is the culprit. For over 20 years now we have been able to recognize this virus by laboratory tests and to find out how much of "clinical flu" it in fact causes. Influenza virus has proved remarkably convenient for laboratory study and has been a more useful tool for theoretical studies of viruses than any other animal virus.

Many virus infections leave behind them a life-long immunity: These are the exanthems and other viruses which during their attack get into the bloodstream. If they ever try to renew their onslaught, they find antibodies in the blood waiting to repel them. Viruses affecting the upper respiratory tract make their attack directly against mucous mem-

branes and do not have to enter the bloodstream to do so. True, some antibody does make its appearance in the mucus covering the epithelium, but it is usually in smaller quantity than in the blood and is less effective. That is probably one reason why respiratory viruses can affect us more than once. In the case of influenza, however, there is another reason. Antibodies in mucus and other defense mechanisms are not wholly ineffective and a "flu" epidemic probably comes to an end as a result of rising herd-immunity. This duly wanes and apparently sinks to a critical level in about two years. Then, that virus which is antigenically a little bit abnormal, stands a greater chance of overcoming resistance and becoming the ancestor of the virus strains of a new epidemic.

In its behavior in the laboratory, influenza virus shows itself similar in many respects to the virus of mumps. Yet epidemiologically they are poles apart. So far as we know, all mumps viruses are antigenically alike; mumps engenders life-long immunity; it is endemic, at most locally epidemic and does not show regular periodicity. Measles commonly has, like influenza, a two-year periodicity, but for a very different reason: It takes just so long for a susceptible population of sufficient size to grow up.

The periodicity of influenza seems to be linked with emergence of antigenic variants, yet not inevitably so, for it does sometimes happen that a similar strain will turn up in two successive epidemics. "New" virus strains may differ to a greater

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* Presented before the California Academy of Medicine at San Francisco, December 10, 1955.

or lesser extent from earlier ones and it may be that variations in the magnitude of the change determine the fact that the intervals between epidemics are not perfectly regular.

Let us briefly consider the nature of the changes which take place amongst "flu" viruses. Although these are very plastic and variable as regards many properties, the changes interesting us now are those concerned with antigenic structure. These are revealed by the hemagglutination-inhibition test. Influenza viruses are readily adsorbed to erythrocytes in fowls and other animals and readily form bridges connecting adjacent erythrocytes and causing their agglutination. Viruses neutralized by antisera are not so adsorbed and do not agglutinate erythrocytes. The activity of sera in thus inhibiting hemagglutination forms the basis of quantitative analysis of their make-up. Further refinements are introduced by using antibody-absorption techniques.

It is easy to show that the two influenza viruses *A* and *B* are serologically unrelated, and that greater or lesser degrees of kinship exist amongst *A* strains isolated in different years. The changes in the virus are important, first in giving us insight into the truly fascinating epidemiologic features of the disease, and second in relation to the question of vaccination. For both these reasons it seemed essential to study the vagaries of influenza on a world-wide basis.

In 1947 the World Health Organization (WHO) set up a network of influenza laboratories based on a World Influenza Center at the National Institute for Medical Research in London, and on a similar laboratory in New York. The idea was this: That information as to the doings of influenza all over the world should be collected at these laboratories and at WHO in Geneva; and that strains should be collected, studied and distributed, so that we could gain knowledge of the relation between antigenic changes and epidemic behavior. A particular question, also, required an answer: Do "flu" epidemics really travel from country to country as appears on the surface, or do outbreaks, arising intrinsically within a country, happen in succession, giving an appearance of geographical spread?

It will help us to answer this question if we consider the history of influenza since, in 1933, the virus was first transmitted to ferrets and so made *amenable* to study in the laboratory. Things have changed a lot since 1933. We use ferrets very little now, mainly to make antisera. As new techniques have been developed, we have seen interest transferred to mice, to amniotic and allantoic cavities of eggs, and to hemagglutinin tests *in vitro*; and finally it has been reported that viruses can be more readily isolated in tissue cultures of human or monkey kidney than by any other means.¹⁰

Viruses from the earlier years of "flu" research, that is 1933 to 1943, were isolated in ferrets and then adapted to mice. These procedures are now thought possibly to affect the antigenic stability of "flu" viruses. We cannot therefore say with confidence anything more than that those strains were very distinct from those of later years. In 1943 a vaccine trial made in the United States gave results indicating a possible four-fold reduction in "flu" incidence in vaccinated groups compared with controls.⁷ Unfortunately, in California the results were less satisfactory than in the rest of the country.⁶ We all hoped that control of influenza by vaccines was in sight. But, alas, the next trial, in 1947, showed hardly any benefit at all from vaccination either in Britain¹⁸ or America.⁸ It soon appeared that a new antigenic type had appeared and was dominating the scene. It had first shown itself in Australia in 1946, but by 1947 was widespread both in North America and Europe. Being so different from the old *A* strains, it was christened *A*-prime (*A'*). This name was, for a number of years, a useful one, as it served to distinguish the older from the newer virus strains. It has, however, outlived its usefulness, for influenza *A* viruses have been progressively changing in their make-up, both before and after 1947, and there is no particular merit in arbitrarily giving a special designation to post-1947 viruses. All are *A* viruses and their changes will doubtless go on. A WHO Expert Committee recommended that prevalent strains of different years should be grouped around a suitable representative, such as FMI of 1947, and referred to as of the such-and-such type. Heaven preserve us from *A*-double prime ... octuple prime, and so on!

Soon after the World Influenza Center got started, an epidemic of influenza broke out in Sardinia and soon "spread" to the mainland of Italy and right across Western Europe, even up to Iceland (Chu, Andrewes and Gledhill, 1950).⁴ Strains received at the Center in London were of one serological type and it was hard to avoid the conclusion that one was witnessing spread of a particular virus infection. This was in the winter 1947-48. In 1948-49 we had the usual welcome absence of an outbreak, and then in 1950-51 another one came along. This showed several interesting features. The main outbreak was preceded, in May 1950, by a late spring local prevalence in Sweden. Nothing was detectable in Scandinavia between June and September, although a special watch was kept; but it was in Scandinavia—Denmark and Sweden—that the main epidemic began in October 1950. Viruses isolated then were of the same serological type as in the flurry of the previous May. Britain apparently had what we may call two concurrent epidemics that year, for a week or two after the Scandinavian virus

hit us, a particularly virulent form of influenza appeared in Liverpool and Belfast and killed many elderly and infirm people. The virus responsible was of a different serological type from the Scandinavian. We named it Liverpool type. This type prevailed in countries bordering the Mediterranean, and subsequently crossed the Atlantic to cause such "flu" as you had in 1951. Our laboratory studies revealed that this Liverpool virus had been present some months ahead of the outbreak in Australia and South Africa. Possibly it had been incubating in the southern hemisphere's winter, ready to cross the equator for its winter sports in Europe. Our experiences in 1951 made us suspect that both of two rival theories of the origin of "flu" outbreaks might be true. The Scandinavian virus must, we felt, have been latent in Scandinavia during the summer, waiting for the right stimulus to activate it; then it must surely have spread across the North Sea and elsewhere, just as the Liverpool type apparently came up from across the equator.¹¹

In 1953 came our next influenza experience, and now the pattern was still harder to define. The viruses we received at the Center were of the same types as in 1951, some much like the Scandinavian, others indistinguishable from the Liverpool, but there was much more suggestion of activation of latent viruses and less of orderly spread. Influenza appeared almost simultaneously in Europe, North America and Japan and the main viruses in all three places were of the Scandinavian type. From a few countries, notably Portugal, we obtained predominantly Liverpool type viruses, but the Liverpool one seemed to be on the way out, and the Scandinavian on the way in.¹³

In the spring of 1955 we expected another major influenza *A* wave in Europe, but it did not come. What "flu" we did have was due to virus *B*. Quite late in the spring, however, odd *A* cases began to turn up—in southern Ireland, South Wales, a few in England; and we had strains from Albany, New York, and from India. From all the places I have mentioned we obtained similar viruses of a rather new type, although there were some of the Scandinavian type as well and a lone Liverpoolian from Lisbon. These small spring outbreaks soon subsided. If we follow the precedent of 1950-51 and of several other years, we may expect outbreaks somewhere this coming autumn and they may very well prove to be due to this (1955) type.

If this guess proves correct, our attention will be drawn once again to a puzzling phenomenon. Here we have the same, or very similar, new types of virus turning up simultaneously in such far distant places as Albany, New York, Ireland and India; turning up, moreover, in the absence of a widespread outbreak. We might explain it on one of

two hypotheses, both of which need careful attention.

1. Hypothesis of Independent but Similar Mutation

Numerous investigators have noted that if influenza viruses are cultivated in eggs in the presence of doses of antiserum insufficient to neutralize them completely, the viruses will change in their properties. This change may turn them into what Dutch investigators call Q-variants, the reactivity of which against all antisera has been reduced (van der Veen and Mulder, 1950).²³ Such a change, it has been suggested, may occur naturally to influenza viruses at the tail-end of an epidemic when herd resistance is high, and a virus may emerge having greater possibilities of survival during hard times. My colleague, Isaacs, suggested that viruses in the Q phase may be turned inside out, so that their more reactive antigenic component is in the middle and some blander, more inoffensive constituent faces the outside environment (Isaacs, Depoux and Fiset 1954).¹²

Magill¹⁷ recently (1955) reported that by passing viruses in partly immune mice he can obtain antigenic variants which are not merely Q-variants but have their antigenic make-up radically altered. There is even a suggestion that if a strain is passed in mice made immune to more than one old strain, its mutation can be pushed in a novel direction, with resulting emergence of a virus resembling that causing a later epidemic. This suggests wild ideas of being able to presynthesize, as it were, in the laboratory the virus which is going to cause the next epidemic and the next epidemic but one. We should then, indeed, be able to be ready with the right vaccines. The idea, however, implies that a novel mutation imposed upon a virus by an unfavorable environment of resistant hosts must go in one particular direction; that a particular antigenic make-up, *Y* is a necessary evolutionary next step following the collapse of its predecessor, *X*. If this were so, it would be easy to see why, as the Liverpool type of virus receded, the Scandinavian one "took over" simultaneously in America, Europe and Japan in 1953. Also why a new type independently appeared simultaneously in Albany, Ireland and India. Yet I confess I find it hard to believe in "chemical evolution" of influenza viruses over a period of years in an inevitable, predetermined direction. The coexistence of similar strains over the whole world is, however, an undoubted fact, and one can hardly imagine that they have evolved quite independently.

2. Hypothesis of Underground Spread

One has, therefore, to consider another possibility. We do not know where influenza *A* virus

persists between epidemics. Most people believe it goes, metaphorically speaking, "underground." It is rarely recovered from "flu"-like illnesses between epidemics. There is a strong suggestion, however, that it can persist in an area without causing outbreaks. I have mentioned the 1950 May outbreak in Scandinavia, followed by a big epidemic starting in the same area the following October and due to a similar virus. One can hardly doubt that the virus was somewhere, locally, "underground" between May and October. More concrete evidence is supplied by Jordan and co-workers¹⁵ in Cleveland who had a population kept under close observation and obtained specimens of serum at intervals. They detected, in individuals, rises in antibodies against influenza A occurring in the absence of "flu" outbreaks or even in the absence of clinical illness in the persons concerned. Now, if influenza can cause such inapparent infections and if we believe, as I think we must, that between epidemics it is in an altered relatively avirulent state, can we imagine that it can nevertheless spread widely? In fact, can a new type of virus travel "underground" from India to Ireland and Albany and be thus widely seeded, ready to cause another epidemic when the time is ripe? If we believe this, we may as well believe that an epidemic such as that spreading across Western Europe in 1948-49 was due to a virus previously seeded across the continent and successively activated in different countries, not spreading in the epidemic form. I do not, honestly, care very much more for my second hypothesis than for my first; it would seem much easier for a virus to spread actively as an epidemic than to crawl about underground doing nothing in particular.

I therefore put forward a third hypothesis which seems to me better to cover the facts. I can believe that in the face of a herd specifically resistant to it, antigenic change in a virus is likely to go, for at least one step, in a particular direction, yielding a particular variant. What I cannot believe is that one could foresee a whole succession of steps along a preordained line, causing parallel evolution of viruses all over the world for a number of years. Again, I can believe that virus goes underground and perhaps does so all over the world, causing odd subclinical infections and not much more, but able to become active and epidemic when the time is ripe. But again, I cannot believe that in this emasculated condition it can effectively spread from India to Ireland and Albany. Indeed, Jordan, in the studies just cited, found no suggestion, from serological studies, that there was such a thing as an epidemic of subclinical influenza.

There is, I suggest, an escape from our dilemma. The virus must be able to loose itself from its re-

straint and get going in epidemic form, with difficulty and infrequently. Thus, it apparently failed to do so anywhere for the great part of the 1954-55 winter. Yet, when it does loose itself, it ravages a large part of the world within a few months. Let us accept what we see at its face value and admit that the country-to-country spread is a genuine phenomenon. It ensures that over a large part of the globe the population is well seeded with one, or a very limited number, of antigenic types of virus. In due course the outbreaks subside and virus persists, if at all, in a relatively avirulent state. Again, in due course, circumstances come to favor an epidemic, and the virus strains which are able to initiate one will be those which have undergone antigenic variation. In populations having in their sera a given antibody-spectrum against older "flu" viruses, the direction of mutation may, for one step, be similar in various places, and thus it is not surprising that similar new antigenic types turn up in Ireland, Albany and India. Some one or more of these gets started earlier or shows greater powers of spread and a new epidemic starts. Other slightly different mutants may arrive here and there but they will be swamped by the flood of the one or few really successful strains, and thus will be preserved in the antigenic make-up of our influenza A viruses the world harmony that we should like to see in other fields. To offer an analogy from the bacteriology laboratory, all bacteriologists know that on plating a specimen on ordinary agar plates they may obtain a mixed culture of all sorts of organism; but let there be one "swarmer" such as *Proteus* and everything else will soon be swamped and next day a loopful taken at random will give *Proteus* in almost pure culture. It is a pity that influenza virus A is so likely to look upon whole continents as agar plates prepared for its benefit.

Undoubtedly variants of influenza virus do turn up which lack what it takes to start an epidemic. Odd strains reach our laboratories in London at times—we had one from Japan, for instance in 1953—strains standing well apart from others in their antigenic characters, and yet we hear no more of them. They either lack power to spread or power to persist when things are against them, or they are smothered soon after birth by a really efficient rival strain.

Just as some new variants fail to survive, so we must explain the apparent extinction of older strains by the very successful competition offered by the really successful "spreaders." Claims to have isolated in recent years viruses like the old classical W.S. and PR8 strains can be accounted for by the

unfortunate facility which laboratory strains have for turning up as "contaminants." Fortunately, these old strains have characteristic "markers," particularly their virulence for mice, so that fallacies can be readily recognized.² There is no good evidence that *A* strains like those of ten or more years ago are current at present.

This brings me to considering some very important results from Ann Arbor, from Francis, Davenport, Jensen and their colleagues. It has been known since the earliest days of work with "flu" viruses that the serological response to infection was, in children, much more specific than in adults. Children would produce antibodies almost only to the currently infecting strain, adults to all sorts of strains. Davenport⁵ and co-workers (1953), studying the matter more deeply, have confirmed these results and carried them further. They have propounded what they call "the doctrine of original antigenic sin": They adduce evidence that human beings produce good antibodies to the "flu" virus they first encounter; on subsequent contact with dissimilar viruses they tend to show an antibody rise to the virus they first met and to respond comparatively much less to the new virus. Even when a response to vaccination is concerned, antibody tends to rise especially high against the virus of the original antigenic sin or contact. From examination of sera of different age groups, one can thus read, as it were, the history of influenza, finding, for example, high antibodies against PR8 in persons over ten years of age and very low antibodies to that strain in young children. Conversely there will be the best antibodies to modern strains in children.

It was suggested long ago by Laidlaw and by Shope that the virus of the 1918-19 pandemic was antigenically like Shope's swine-15 strain of swine influenza. You will recall a suggestion that pigs in the Middle West first contracted swine influenza as a result of contact with the human pandemic virus in 1918. It is thus especially interesting that antibody to swine "flu" is particularly pronounced in people who were exposed in 1918. We noted this, in Britain, in 1935,¹ although we were later more dubious about the interpretation of the results. The Ann Arbor workers, however, now strongly support the original thesis.

These findings have a bearing on the "directed mutation" of newly arriving influenza viruses. Magill¹⁷ found that if a "flu" virus were passed in mice partly immune to itself, there was a tendency to revert to an *older* antigenic pattern. If, however, he made mice doubly immune to the current and to the older strain, there was more likelihood that the virus would launch out in a new direction. Today a newly emerging virus will find that younger people have antibody to recently prevalent antigens, while

different groups of older people will have sera reactive against various strains of varying degrees of antiquity. It will thus be able readily to attain epidemic status, only if it can spread freely in people having antibodies to none of the recently prevalent antigens. Clearly, however, it might turn in a circle and hypertrophy an old antigen once the population resistant to that antigen had died out. Francis,⁷ discussing such possibilities in 1945, expressed delight with what he called a "splendid basis for the classical notions of the periodicity of influenza."

It is noteworthy that swine influenza viruses in the Middle West have not changed antigenically as greatly as human viruses have.¹⁰ This might be because the economics of pig-breeding insure that pigs immune to the virus do not survive to hamper the spread of virus in the herd; and the virus is thus not under compulsion to keep changing its antigens.

Here we must pause, lest we be carried along too enthusiastically. People have always been able to perceive an orderly periodicity in influenza epidemics if they have only looked backward; they have rarely been so successful in forecasting the future. There could well be a regular periodicity in the antigenic make-up of successive influenza viruses, having interest only for the laboratory man and of no readily apparent clinical significance. The 1918-19 influenza virus had remarkable properties, particularly the ability to kill young adults instead of the extremes of age as do most "flu" viruses. There is no evidence at all that this property was necessarily tied up with any particular antigenic structure. The 1918 influenza *may* have been antigenically close to swine "flu" virus and that antigenic make-up may one day recur in our human viruses without any return to the catastrophe of 1918. Indeed man is constantly exposed to such a virus, if he raises pigs in the Middle West; and yet he does not apparently catch "flu" from his pigs at all.

We also need to understand more about the significance of cross reactions in antigenic studies of influenza viruses. Jensen and Francis¹⁴ (1953) suggested that there is a small finite number, perhaps eighteen, of "flu" antigens. It is suggested that all the antigens are present in all influenza strains, some in small quantity or deeply buried, one or few at a time being dominant. The conclusions are based on absorption techniques, the significance of which has been disputed by other workers (Takátsy and Fűrész,²¹ 1954). Now that we have had experience of viruses with dominant antigens of these eighteen types, we are, according to the argument, about due to go back to the beginning again.

My colleagues and I feel much more hesitant about interpreting these findings. We feel less convinced that all the past antigens are present in current strains and that no new ones are appearing. We are disposed to wait and see if influenza variation proceeds indefinitely in a straight or sinuous line, or travels in a circle which is due to come round to its starting point fairly soon or not for many many years.

One's ideas on these matters are not purely academic; they influence policy in the matter of the composition of influenza vaccines. The successful use of influenza vaccine in the United States in 1943 raised strong hopes for the future—hopes which the failure of vaccines in 1947 dashed to the ground. Few doubt that the failure was due to the unusually large antigenic changes which virus *A* underwent about 1946-47. At discussions in Britain, we decided that the best hope was to make our vaccines from the very latest strain available plus the latest-but-one. With the appearance of a new type this would be incorporated and the older of the existing two strains dropped. The policy in the United States has been different. It is felt by Francis and his colleagues that a vaccine composed of many antigenic types old and new should give coverage against anything likely to crop up. Which policy one favors will depend not a little on the views one holds as to the structural make-up of virus *A*, the nature of the changes it undergoes and their likely future course. In Britain we are at the moment undertaking a field trial which we hope will decide whether a univalent or bivalent vaccine of recent strains will give better protection than what I will call an American cocktail. A decisive result would give most valuable guidance for the future. It is of course much easier for manufacturers to prepare vaccines from mixtures of old and trusted strains; but if we can only prevent influenza by incorporating new strains, then that is what has to be done.

It is my hope that this presentation will convince readers that time-consuming and intricate studies of the antigenic make-up of influenza viruses have a real practical importance: They may help us to

understand what is epidemiologically a unique and fascinating disease; and they may help us to prevent it from too greatly harming us. Above all, we may learn what to do to prevent a recurrence of what, only 36 years ago, was the most killing plague mankind has ever known.

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The Treatment of Cancer of the Thyroid Gland

L. HENRY GARLAND, M.D., San Francisco

CARCINOMA of the thyroid gland is relatively uncommon. According to the most recent available statistics reviewed by Dorn and Cutler,⁶ the age adjusted incidence of cancer of the thyroid gland in the United States each year is approximately 1.1 per 100,000 males and 3.4 per 100,000 females. In other words the incidence is about 2.3 cases per 100,000 population per annum. Sokal,¹⁴ after an extensive review, also estimated the incidence at approximately this figure.

The usual sex ratio of thyroid cancer is three cases in females for every one in males.

In adults with nodular goiter the incidence of thyroid cancer is stated at widely different rates, ranging from about 0.2 per cent of patients with nodular goiter according to Sokal, through 4.8 per cent of such patients according to Queen,¹³ up to as high as 20 per cent according to some surgical observers.¹⁵ Since the latter usually base their data largely on patients operated upon, while other investigators use data based on a theoretical "total" population sample, it would appear that the true incidence of thyroid cancer in all adults with nodular goiter is distinctly less than four per cent. Sokal expressed belief that thyroid cancer arises more frequently in toxic than nontoxic nodular goiter (the respective percentages being 1 and 0.2). Other observers do not concur. There has been a considerable divergence of opinion as to the incidence of cancer with regard to whether there is a solitary nodule or multiple nodules on the thyroid gland. However, since surgical and microscopic examination of thyroid glands with so-called solitary nodules usually reveals the presence of additional or multiple nodules, this aspect of the problem will not be considered further herein.

The incidence of thyroid cancer in children with nontoxic nodular goiter is reported by Winship¹⁸ to be almost 30 per cent (that is, of those children coming to operation); it is presumably lower in children in general who have that disease, but the exact figure is not known.

PATHOLOGIC CLASSIFICATION

There are almost as many pathologic classifications of tumors of the thyroid gland as there are

Read before the Radiology Society of Southern California, Los Angeles, January 28, 1956.

• The optimum treatment for cancer of the thyroid depends on (a) the pathological type of tumor present and (b) the stage of the disease.

In patients with well-differentiated papillary carcinoma, simple operation is usually adequate. In cases of most other types, more extensive operation, followed by adequate postoperative radiotherapy, is regarded as the treatment of choice. In terms of clinical stage, the primary treatment of most cases classified as Stage I or II should be surgical, and of most cases classified as Stage III or IV, radiological.

The five-year survival rate in a series of non-terminal cases treated under such a program was 47 per cent.

Persistent treatment of selected inoperable or metastatic lesions may result in unexpectedly long survivals.

reports in the literature. For several years the rather detailed classification of Warren was commonly used. Ackerman¹ modified Warren's classification essentially as follows:

- I. Tumors of low or potential malignancy.
 1. Adenoma with blood vessel invasion (fetal adenoma).
 2. Papillary cystadenoma with blood vessel invasion.
- II. Moderate degree of malignancy.
 1. Papillary adenocarcinoma.
 2. Alveolar adenocarcinoma.
 3. Hurthle cell adenocarcinoma.
- III. Higher grade malignancy.
 1. Small cell carcinoma (carcinoma simplex).
 2. Giant cell carcinoma.
- IV. Miscellaneous types.
 1. Epidermoid carcinoma.
 2. Fibrosarcoma.
 3. Lymphoma.

Bell² and others stressed the fact that there are no dependable microscopic criteria for the diagnosis of malignant adenoma. Bell noted that some investigators observed that malignant adenoma recurs in only about 3 per cent of cases even though the tumor may have invaded veins.

In recent years there has been a tendency to classify carcinomas of the thyroid gland as follows:

1. Papillary adenocarcinoma (tumors with papillary or predominantly papillary pattern). Many of these are well differentiated.

2. Follicular adenocarcinomas (tumors with follicular or predominantly follicular pattern — formerly called alveolar).

3. Undifferentiated carcinoma (including tumors which formerly carried such headings as small cell, giant cell, spindle cell and solid carcinomas).

There are of course other primary malignant lesions of the thyroid gland such as epidermoid carcinoma, oxyphilic (or Hurthle cell) carcinoma, malignant lymphoma and sarcoma. These are relatively uncommon. In addition, there are malignant tumors metastatic from other sites, notably the breast and lung, which may be mistaken clinically for primary thyroid cancer even by the most wary.

The approximate incidence of the different pathologic types varies in different reported series. In general, it would appear that tumors of low grade malignancy constitute about 55 per cent of malignant thyroid tumors; those of moderately good differentiation, including follicular tumors, average perhaps 30 per cent of all thyroid cancers, while those of undifferentiated type or high degree of malignancy average about 15 per cent. It is noteworthy that in reports from some surgical clinics, the undifferentiated group accounted for less than 8 per cent of the series treated, while in reports from some radiotherapeutic clinics this undifferentiated group accounted for as high as 51 per cent of the cases treated. It is therefore evidently impossible to compare the overall results of treatment in different institutions in the absence of knowledge of the relative number of the different pathologic types treated.

Winship and Chase¹⁸ recorded the following pathologic types in a collected series of 596 cases in adults studied in recent years (they are listed in the order of increasing malignancy):

Cell Type	Per Cent
Papillary adenocarcinoma	15
Papillary and follicular adenocarcinoma.....	46
Follicular adenocarcinoma	17
Oxyphilic adenocarcinoma	3
Undifferentiated adenocarcinoma	18
Lymphoma	1

In about two-thirds of the mixed papillary and follicular tumors, the papillary type predominated; in the other one-third, the follicular type (which sometimes accepts therapeutic amounts of radioiodine) predominated.

STAGING

Clinical staging of tumors has moderate value both for the planning of treatment and for the estimation of prognosis, notably in the case of cancers of the uterine cervix and the breast. Staging

based on clinical and microscopic observations is of value in dealing with tumors of other sites such as the fundus uteri. There is considerable divergence of opinion in the literature as to the value of staging in thyroid cancer. Some investigators, Winship¹⁸ among them, regard staging as of more importance than the histologic type in estimating prognosis; other observers have the opposite opinion, Jacobson⁸ proposed the following staging based on the clinical and microscopic observations at the time of surgical exploration carried out in patients with thyroid "lumps":

1. Movable tumor without known metastasis.
2. Movable tumor, with mobile unilateral node metastasis.
3. Fixed tumor, or tumor with bilateral or fixed node metastasis.
4. Patient with distant metastatic lesions.

The limitations of either microscopic or macroscopic staging is well illustrated by Ward's¹⁶ prognostic summary:

Five-year survival rates based on clinical and surgical observations:

	Per Cent
1. Carcinoma diagnosed or suspected preoperatively	20
2. Carcinoma diagnosed at operation (gross) ..	40
3. Carcinoma diagnosed first on microscopic examination	80

Kearns and Davis⁹ expressed belief that the histologic appearance of the tumor contributes little to the prognosis. All agree that some relatively well differentiated papillary tumors progress to a fairly early fatal outcome, while occasional undifferentiated tumors are associated with unexpected longevity. Crabtree and Hunter⁴ said that "Deaths from cancer of the thyroid are directly proportional to the ease of clinical diagnosis (*i.e.* the stage) and the degree of anaplasia."

TREATMENT

The primary treatment of most cases of carcinoma of the thyroid is surgical, in order to provide both microscopic diagnosis and potential removal of the lesion. There is wide difference of opinion as to whether the operation should consist of relatively simple excision (lobectomy) or removal of the entire thyroid gland combined with radical neck dissection. Martin¹⁰ expressed belief in the value of thyroidectomy with radical neck dissection, the latter at least on the same side as the lesion. On the other hand, Crile⁵ and many equally experienced surgeons have expressed the opinion that radical neck dissection has not much to offer, pointing out that when metastasis to nodes is present in the case

of well differentiated papillary tumors, the nodes tend to grow slowly and remain with little change in size for many years. On the other hand when such metastasis is present (especially in the case of poorly differentiated tumors), the probability of the surgeon's being able to remove all the involved nodes is slight; many patients with metastasis to cervical nodes also have nodal involvement extending below the clavicle into the mediastinal or axillary areas. Surgical removal of mediastinal nodes has been attempted, but the condition of the patients after bilateral radical cervical and upper mediastinal node dissection is not a very happy one.

The general plan of treatment which the author believes to be wise may be summarized as follows (utilizing the previously described staging):

Stage I and II: Usually surgical. Then, if the tumor is microscopically well differentiated and apparently totally removed, no postoperative radiotherapy; but if the tumor is poorly differentiated or incompletely removed: radiotherapy.

Stage III and IV: Usually radiotherapy (after confirmation of diagnosis).

In general, the most effective way of irradiating the neck and adjacent tissues in the presence of inoperable carcinoma of the thyroid gland is by wide-field roentgen therapy.¹² In many cases a single large anterior field may be used, the field extending from approximately the hyoid bone down to the middle of the manubrium sterni. (The intrinsic larynx is shielded with lead.) Such a field includes both the cervical and upper mediastinal node groups. In suitably built patients, with "thick" necks, two lateral fields may be added. In selected patients, posterior oblique fields, aimed at the thyroid and its lymph node drainage area (but missing the spinal cord) may also be used.

In patients with widespread lesions of a follicular type, which accept radioactive iodine (perhaps 2.5 per cent of all patients with cancer of the thyroid gland) radioiodine should be used.

The usual plan of treatment is to attempt to deliver a midtumor dose of approximately 4,000 r in about four weeks, using orthovoltage radiation with a half value layer of 2 mm. copper.

It is believed that 4,000 r of 250 kilovolt radiation with the half value layer of 2 mm. of copper is biologically equivalent (in terms of effect on cancer in humans) to about 6,000 gamma roentgens from a telerradium, telecobalt or megavoltage source. Most adult patients will tolerate this dosage to a wide field in a four-week period without serious permanent after effects. If heavier dosage to large areas is given, undesirable late sequelae are likely to occur. On the other hand, sharply localized persistent areas

of disease may sometimes be treated with small fields to a tumor dose of about 6,000 x-ray roentgens in four weeks, but cases suitable for such therapy are exceptional.

The radiosensitivity of thyroid cancer in the individual case cannot be predicted. It can only be determined by a trial of adequate radiotherapy. In general, it would appear that:

1. Most tumors of predominantly papillary type are moderately radiosensitive;
2. Tumors of predominantly follicular type are radiosensitive in about one-half the cases; and
3. Tumors of undifferentiated type are usually radiosensitive, but unfortunately incurable because of early generalized metastasis.

Metastatic disease in the lungs, bones, brain and distant node sites may be treated by roentgen therapy or radioiodine according to the nature of the case and the presence or absence of iodine-accepting tumor tissue. Unfortunately, only the adenocarcinomas with colloid formation (follicular tumors) take up enough radioiodine to be affected significantly, and even those that do accept the iodine do not take it up homogeneously.¹¹

In general, only about 50 per cent of patients with cancer of the thyroid gland have "operable" lesions when first observed (Cohen and Moore),³ and since it is exceptional to be reasonably sure that all of the tumor has been excised, careful postoperative radiotherapy should be carried out in most "operable" cases. The kind of tumor present is probably more important in the determination of ultimate survival than the extent of the operation or the intensity of the radiotherapy applied.

RESULTS OF TREATMENT

The author's personal experience with cancer of the thyroid gland is small: Between the years 1930 and 1952, 23 patients were observed in consultation at the San Francisco Hospital and 19 patients in private practice, a total of 42 cases of "validated" cancer of the thyroid gland.

The pathological classification and clinical staging of the patients were not uniform during this period. Indeed, there were 31 cases indexed as *carcinoma of the thyroid* in the San Francisco Hospital files up to 1952, but upon review it was noted that in eight of the cases the patient did not have primary thyroid cancer. These eight were as follows:

Carcinoma of the thyroid gland, metastatic from lung, one case.

Carcinoma of the thyroid gland, metastatic from an undetermined primary site, three cases.

Adenoma benign (reviewed diagnosis), two cases.
Error in tumor registry, two cases.

These eight cases are not included in the subsequent discussion.

The pathological classification employed at the time of preparation of this summary was as follows:

1. Papillary carcinoma and other well differentiated tumors (such as so-called malignant adenoma).

2. Adenocarcinoma, unspecified or moderately well differentiated.

3. Undifferentiated carcinoma (and carcinoma, type unspecified).

It is now apparent that this classification is neither as clear nor as logical as that listed previously in this paper. However, it will be used in presenting the results to date.

The staging was based on that of Jacobsson and was done retrospectively after a review of the clinical, surgical and microscopic records.

The treatment consisted of surgical operation alone in the cases of papillary tumors which had been apparently completely removed, of operation plus postoperative roentgen therapy in the other operable cases, and of radiotherapy alone in the nonterminal inoperable cases. The surgical operation was usually conservative (lobectomy). In some cases it consisted of biopsy only; in others, total thyroidectomy was done. The postoperative radiotherapy was moderately intensive in patients whose clinical condition permitted (the aim being to give a midtumor dose of about 4,000 x-ray roentgens in some four weeks' time). It was usually merely palliative or even only token in amount in the advanced or terminal cases.

Of the 14 patients known to have survived over five years, 11 received postoperative radiotherapy.

Of the 28 patients who did not survive five years (including the three cases in which follow-up information is not available), 15 received postoperative radiotherapy. Many of the group who did not receive treatment were in terminal stage. Some of them had little more than biopsy or tracheotomy.

Of the 15 adequately followed patients who were not in terminal condition when first observed, 11 received postoperative radiotherapy and four did not. The average survival time in both groups was quite similar (about 22 months) despite the fact that the patients given radiotherapy were a much less favorable group. Most of the patients referred for postoperative radiotherapy had obvious persistent or inoperable tumor; two of the four not referred were believed to have had successful removal of tumor, and the other two were found to have widespread metastatic lesions shortly after opera-

tion. Objective evidence of radiotherapeutic benefit included shrinkage of palpable masses, improvement in swallowing and decrease in size of radiographically visible lesions. The most frequent reason for ultimate failure was the undifferentiated nature of the tumor present.

Pathological classification of cases:

Type (see text)	San Francisco Hospital	Private Office	Total
Papillary carcinoma	5	6	11
Adenocarcinoma	4	5	9
Undifferentiated carcinoma	14	8	22

Clinical staging of cases:

Stage	San Francisco Hospital	Private Office	Total
I	4	2	6
II	2	7	9
III	5	7	12
IV	12	3	15

Record is available of 39 of the 42 patients either to death or for over five years. The three untraced patients are counted as dead of disease in the final tabulation, although in two of them the disease was classified as Stage I and they were living and well some years (but less than five years) after operation. In the other patient lost to follow-up before a full five years had elapsed, the classification was Stage II.

The five-year survivals according to pathologic type are as follows: Papillary carcinoma, eight of eleven patients; adenocarcinoma, moderately differentiated, two of nine cases; carcinoma, undifferentiated or unspecified, four of twenty-two cases.

It is known that long survivals in undifferentiated carcinoma of the thyroid gland are so rare as to raise reasonable doubt concerning the pathological classification of such cases. Only one of the four patients in this small series who survived for such a period had a diagnosis of undifferentiated carcinoma; the remaining three had unspecified or unclassified carcinomas, without clear information as to the predominant type of cell present.

The five-year survivals according to the clinical and microscopic stage of disease were as follows:

Stage I: Four of six patients are known to have survived; (two not traced).

Stage II: Six of nine patients are known to have survived; (one not traced).

Stage III: Four of twelve patients survived.

Stage IV: None of 15 patients.

It should be noted that two of the patients died not of thyroid cancer but of cardiac disease. However, they died within the five-year interval and theoretically might have had recurrence had they lived. Conversely, two of the patients who did survive five years, had recurrence after that time (one at six and one at seven years) and died of cancer.

In all, 14 of 42 patients (33 per cent) survived five years. Twelve of the 42, were actually in terminal condition on admission and died of cancer within a few weeks. Excluding this hopeless group (to which neither curative operation nor radiotherapy was applicable) 14 of 30 patients survived five years (47 per cent).

As was previously noted, three of these survivors were treated by surgical operation alone and 11 by operation and radiotherapy. The three treated by operation alone were as follows:

1. A man 40 years of age. Subtotal thyroidectomy for papillary adenocarcinoma (pathologically, malignant adenoma). No postoperative roentgen therapy. After five years recurrence developed in neck and then bony metastasis. Palliative roentgen therapy was given. The patient died in the sixth postoperative year.

2. A 65-year-old woman. Thyroidectomy for "malignant adenoma" with capsular invasion. Later pathologic diagnosis: Papillary adenocarcinoma. Postoperative roentgen therapy advised, but patient was discharged before it was administered. Living to date (five years).

3. A woman 49 years of age. Hemithyroidectomy for moderately differentiated adenocarcinoma. No postoperative roentgen therapy. After three years questionable scapular metastasis developed. Radiotherapy was given. Living five years postoperatively.

PROGNOSIS

Prognosis in individual cases of cancer of the thyroid gland is difficult. Kearns⁹ reported a patient who had thyroid carcinoma for 35 years yet was clinically well. Crile⁵ noted a similar case. The patient was well for over 25 years without treatment. The diagnosis was made by cervical node biopsy. Ward¹⁵ reported a patient who had goiter at age 24. It was present for 26 years before operation, was resected three times and treated with radiotherapy, and finally caused death at age 68. Ward asked: "Was the tumor malignant for 44 years, or for only about 20 years?"

One of the patients in the present series, a woman 22 years of age with undifferentiated carcinoma of the thyroid gland, had subtotal thyroidectomy (the clinical diagnosis was thyroiditis or "Hashimoto struma"). Two experienced pathologists interpreted the removed gland as undifferentiated carcinoma. The surgeons suspected that they had "seeded" the neck area and that reoperation would be futile. An immediate postoperative course of roentgen therapy to a tissue dose of approximately 4,000 r in four weeks was given. It was the author's impression and

that of the surgeons that the prognosis was hopeless. However, when last observed six years later, the patient, the mother of two children, was clinically well and without evidence of tumor or undesirable skin changes. Hers is regarded as an exceptional case.

In general, there is good prognosis for long survival with well-differentiated papillary adenocarcinomas, but startling exceptions do occur, and "indolent" tumors may become aggressive, especially in metastatic lesions.

With undifferentiated carcinoma of the thyroid gland the prognosis is virtually hopeless. Most patients are dead within a year of histological recognition.

Tumors of moderate differentiation are often associated with long survival especially when vigorous surgical and radiological means are employed to control the various manifestations of the disease as they appear. Diffuse pulmonary and nodal metastatic lesions may prove sensitive to roentgen therapy; bone lesions frequently heal; persistent efforts by the attending physician may yield great dividends in cases of this type. Radioiodine may occasionally be of much help.

MORBIDITY OF RADIOTHERAPY

Radiotherapy, like surgical treatment has its morbidity. With care and experience this can be kept to a minimum. It includes early erythema and dysphagia, and late telangiectasis, atrophy, fibrosis and ulceration. More serious complications include fistula and hemorrhage. Surgical morbidity includes bilateral recurrent laryngeal paralysis, postoperative hemorrhage, hypoparathyroidism, esophageal fistula and severe debility (which sometimes follows ultraradical procedures). Radical radiotherapy is rarely feasible or wise after radical operation.

Late undesirable radiotherapeutic effects can be kept to a minimum by careful individualization of treatment, avoidance of unduly rapid dosage, especially in the presence of infection, and scrupulous attention to technical details. When the radiotherapist himself performs each irradiation procedure he is in the best position to individualize carefully. Unduly protracted courses of irradiation, repeated heavy irradiation, and too rapid dosage in the case of debilitated persons all should be avoided.

In selected cases, ultra-hard radiation may be indicated. However, devices such as convergent beam therapy, rotation therapy, grid therapy and attempted tumor sensitization with drugs like synkavit have not been reported as effective.

DISCUSSION

The optimum place of radiotherapy in the treatment of cancer of the thyroid gland is the subject of considerable controversy. Most surgeons appear to agree with Martin¹⁰ that it is indicated for "rapidly growing, inoperable, and locally recurring thyroid cancer" and for "painful osseous metastases"; but several add the comment that its post-operative use is not usually indicated. This paradox is presumably owing to the fact that much surgical writing deals with the operable cases in which *all* the tumor has been apparently removed, the writer ignoring or forgetting the many cases in which it is unfortunately not possible to dissect all the tumor from the trachea or remove all of the involved nodes.

Martin objected that "no evidence has ever been presented that radiation alone has produced five-year cures of thyroid cancer," apparently ignoring the five-year survivals in inoperable cases reported by Windeyer,¹⁷ Jacobsson,⁸ Paterson¹² and others. These five-year survivals in good health are just as much clinical cures as five-year survivals after surgical operation alone. In both instances, many of the patients would probably have survived five years anyway—because of the biological type of cancer present. However, in some cases the definitive radical therapy (radiological or surgical) unquestionably removed or destroyed hazardous masses. The author believes that except in the case of well differentiated papillary tumors apparently completely excised, the weight of clinical evidence is in favor of postoperative radiotherapy.

Survival or cure rates are always difficult to analyze. Most reports of surgical results are based on the operable cases seen and followed; they are relative, not absolute, results, and often exclude patients with inoperable lesions, those who refuse operation, those who died of intercurrent disease within five years and those who were lost to follow-up. Reports of radiotherapy results tend to be based on patients who were inoperable at the time of diagnosis or in whom the surgeon felt that some tumor had been left behind. They are strictly not comparable with surgical results in the more favorable series of operated cases. However, as in the case of surgical reports, some radiotherapists exclude cases in which the patient died of intercurrent disease or in whom completion of treatment was not possible, and few published results are "absolute"—that is, based on all patients seen, whether treated or not.

Recurrences may appear after such long periods of quiescence that Winship and Chase,¹⁸ for example, would prefer results to be based on 20-year

follow-up. They therefore disagree with Martin in his rather astonishing observation that "To be of practical value, end results . . . cannot very well be calculated on the basis of an observation period of much more than 5 years—otherwise by the time the figures were calculated, a great proportion of the active surgeons would have died of old age or be in retirement, in which case few surgeons could improve their methods by a critical analysis of their own experience and results."

Horn and Dull⁷ noted that five-year survival of 59 per cent (of 112 cases) dwindled to ten-year survival of only 30 per cent—and three of the latter group of patients had known recurrent disease. It is to be noted that in two-thirds of the cases in the group reported upon, the lesions were detected microscopically. The five-year survival rate for the patients in whom cancer was diagnosed clinically was only 37 per cent.

The following are other recently published five-year survival rates:

Windeyer¹⁷ (London University-Middlesex Hospital): 37 per cent.

Cohen and Moore³ (University of Minnesota)*: 34 per cent.

Jacobsson⁸ (Radiumhemmet, Stockholm): 46 per cent.

Martin¹⁰ (Memorial Hospital, New York): 42 per cent.

On the other hand (and to illustrate the results obtainable with material doubtless less favorable than the above) Watson and Pool¹⁶ reported five-year survival of only eight per cent. Presumably their series contained a much larger proportion of cases of undifferentiated or advanced cancers than those of the other quoted investigators whose papers were published in more recent years.

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Surgical Treatment of Pulmonary Tuberculosis

A Decade of Change

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REVOLUTIONARY CHANGES have occurred in the treatment of pulmonary tuberculosis during the past ten years—the more striking by contrast with the gradual evolution in previous decades. The anti-tuberculosis drugs have greatly altered the treatment, the prognosis and, to a lesser extent, the attitude of physicians caring for tuberculous patients. The effect that the chemotherapeutic revolution has had on the surgical treatment of tuberculosis was noted in a review of surgical trends in the last ten years at the San Diego County General Hospital's Tuberculosis Division (Vauclain Home). The trends observed are a reflection of the opinions of the staff of the Tuberculosis Division, since surgical therapy is based on decisions of a combined medical and surgical conference.

The discovery of streptomycin introduced a drug with specific activity against the tubercle bacillus. The drawbacks to its use were gradually overcome by the addition of para-aminosalicylic acid, by the prolongation of the course of streptomycin and by reduction of the dosage to 1 gm. twice weekly. Long term drug therapy became even more common after the introduction of isoniazid. The antituberculosis drugs, which at first were used as supplements to other forms of therapy, are now primary means of treatment. Today almost without exception patients with active tuberculosis are immediately started on drug therapy, which is continued at least a year and, for most patients, several years. The increase in the use of the antituberculosis drugs during the last ten years is illustrated in Chart 1.

During the ten-year period 1945-1954, the mortality in San Diego County from tuberculosis dropped from 23 to 6.7 per 100,000 population, the swifter drop occurring after 1950 (Chart 1). The hospital's mortality rate as to patients with tuberculosis also dropped: In 1945 30 per cent of patients discharged from the Tuberculosis Service died; in 1954, 7 per cent (Chart 2).

The widespread use of long-term drug therapy has also produced a decrease in the average hospital stay of hospitalized patients and an increase in the number of patients under active treatment at home. This has resulted for the first time in the closing of

• To observe trends in the surgical therapy of pulmonary tuberculosis, the records of patients treated during the last ten years at the Tuberculosis Division of the San Diego County General Hospital (Vauclain Home) were reviewed.

In this decade, a chemotherapeutic revolution permitted more patients to be treated with fewer beds, lower mortality and shorter hospitalization.

Pneumoperitoneum has replaced other forms of temporary collapse. Pneumothorax, phrenic nerve interruption and pneumonolysis have been abandoned in favor of extrapleural plombage, particularly in older, poor risk patients.

The use of permanent collapse measures as definitive treatment has decreased, thoracoplasty and extrapleural pneumothorax having been virtually abandoned.

The use of resection in patients with permanent collapse failure, residual cavities, broncho-stenosis and destroyed lobes or lungs has become common, and good results have been obtained.

sanatorium beds and the disappearance of a waiting list (Chart 3)—this despite the fact that the number of patients treated in sanatoria actually increased in the decade covered by this study. More entered the Tuberculosis Division but they stayed a shorter time (Chart 2). In short, more patients are being treated, with a lower mortality rate, with fewer beds and shorter hospitalization.

TEMPORARY COLLAPSE MEASURES

The chemotherapy revolution has greatly altered the attitude of the staff toward the temporary collapse measures. Pneumothorax and phrenic nerve interruption are no longer used. Pneumoperitoneum has replaced them. During the last seven months of 1954 no pneumothorax refills were given and the last initial pneumothorax was in September, 1953 (Chart 4). This change in attitude has been brought about by the fact that with pneumoperitoneum there are practically no pleural complications and the condition is completely reversible from the functional standpoint. Also, when used in conjunction with drugs, pneumoperitoneum was found to be almost as effective in cavity closure as good pneumothorax. The change in use of temporary collapse measures

Submitted October 10, 1955.

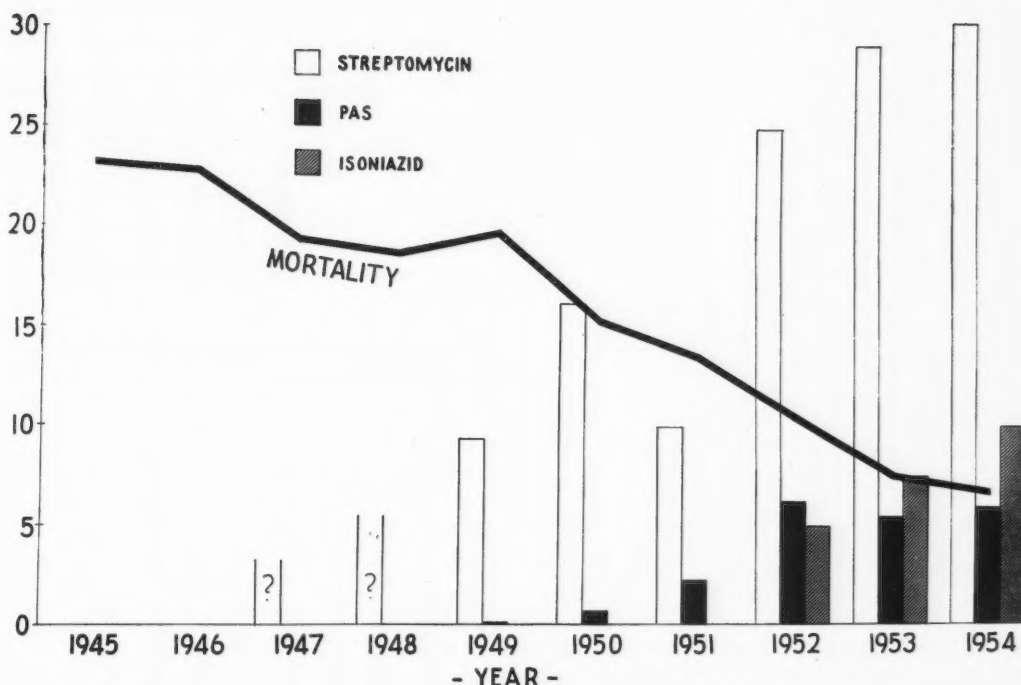


Chart 1.—Deaths from pulmonary tuberculosis per 100,000 population in San Diego County related to drugs purchased at the San Diego County General Hospital. Streptomycin and isoniazid purchases are shown in kilograms and para-aminosalicylic acid (PAS) in 100 kilograms. (Records are not available for drugs purchased during 1947 and 1948.) The decrease in streptomycin purchased in 1951 was due to a shift from daily to twice a week schedule in its administration as the use of PAS increased.

has thus made phrenic nerve interruption and pneumonolysis obsolete as minor surgical procedures (Chart 5).

PERMANENT COLLAPSE MEASURES

Permanent collapse measures which constituted the backbone of surgical treatment of tuberculosis as recently as 1950, have now been relegated to a secondary role since the advent of drugs and resective operations.

Thoracoplasty

During the last decade the two or three stage, seven-rib thoracoplasty has practically been abandoned. Patients who formerly would have had this form of permanent collapse therapy, now have closure of pulmonary cavities with chemotherapy and perhaps pneumoperitoneum, and are either spared operation or have resection. During the seven-year period prior to 1952 a yearly average of 22 patients had definitive thoracoplasty operations, the great majority having seven or more ribs removed in multiple stages. Since 1952 a total of only ten patients have had definitive thoracoplasty, all having five or less ribs removed, except one who had a one-

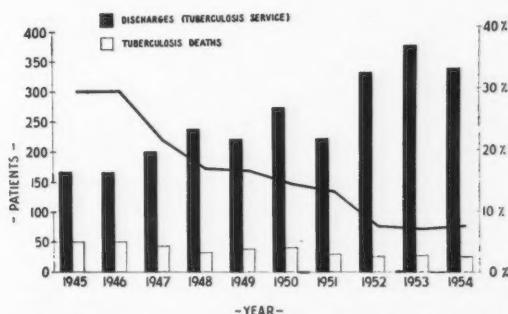


Chart 2.—Discharges from the San Diego County General Hospital, Tuberculosis Service and the number of deaths from tuberculosis among the discharges. The percentage column at the right shows the ratio of deaths to discharges.

stage six-rib thoracoplasty. In 1954 only two patients had definitive thoracoplasty (Chart 6).

Thoracoplasty of five or less ribs has been used after resection or (rarely) at time of resection in order to reduce space and promote expansion of remaining lung tissue. Six-rib thoracoplasty, sparing the first rib and including the seventh rib, has been used routinely after pneumonectomy in patients who had not previously had thoracoplasty.

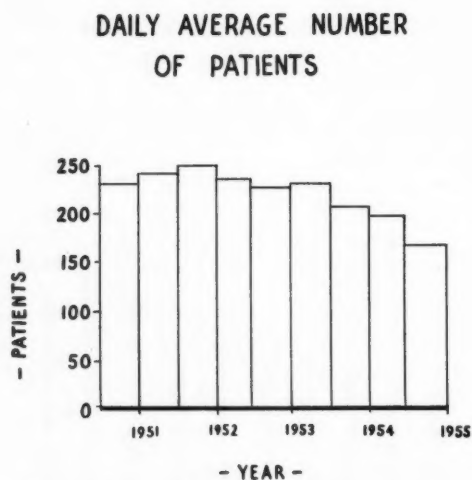
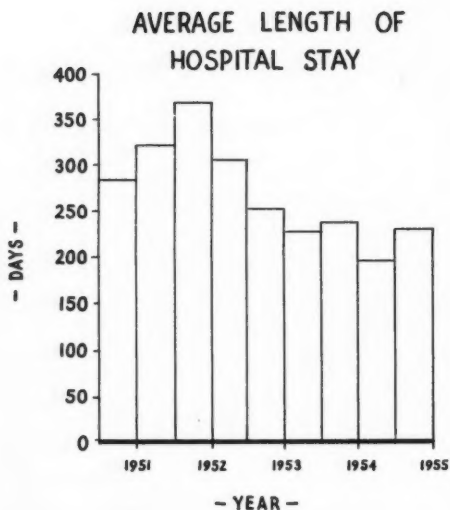


Chart 3.—Upper: Average length of hospital stay of adult tuberculosis patients at the San Diego County General Hospital between June, 1950, and January, 1955, by six-month periods. Lower: Daily average number of patients of same classification.

Revision thoracoplasty was rather commonly used during the first five years of the decade, but has been little used since 1950. The mortality rate has been low in the thoracoplasty series, there having been no deaths since 1948 attributed to that operation. Of the last 50 patients operated on since 1950, four are dead. Three of them died of non-tuberculous causes and one, in whom thoracoplasty failed, had resection and died following that operation.

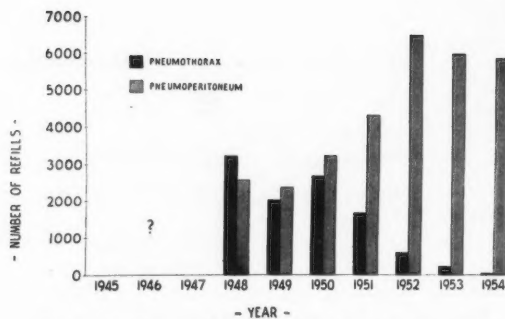


Chart 4.—Pneumothorax and pneumoperitoneum refills, both in-patient and out-patient, at the San Diego County General Hospital.

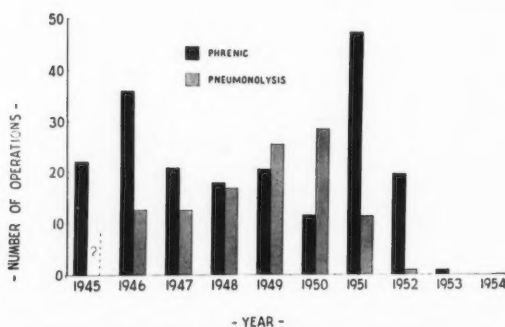


Chart 5.—Phrenic nerve interruption operations and closed pneumonolysis operations by years, during the decade of 1945 through 1954, at the San Diego County General Hospital. Neither operation was done in 1954.

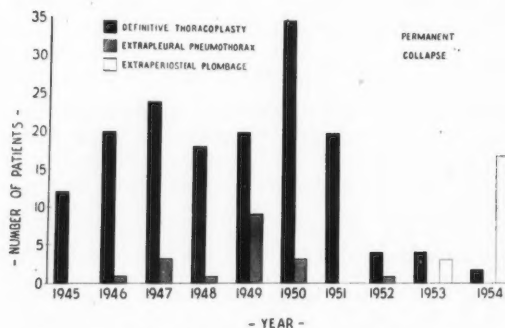


Chart 6.—The use of three "permanent" collapse measures during the decade of 1945 through 1954 at the San Diego County General Hospital.

Extrapleural Pneumothorax

Extrapleural pneumothorax, a more or less permanent collapse measure which has never been widely employed in this country, has been little used at Vaulain Home. Only 18 patients have had that operation in the last decade—nine of them in 1949, and only one since 1950 (Chart 6).

Extraperiosteal Plombage

Since the summer of 1953 extraperiosteal plombage⁹ (with lucite spheres covered with polyethylene sheeting) has been used in increasing numbers. The advancing average age of patients at the sanatorium—40 per cent of males discharged in 1954 were over 55 years of age, compared with 26 per cent in 1945—has increased the demand for an effective means of treating chronic cavitary tuberculosis in older, poor risk patients in whom the risk of resection appears to be prohibitive. Extraperiosteal plombage appears to be superior to thoracoplasty in patients of this type. It is performed in one stage with selective collapse effectively applied without paradoxical motion of the chest wall during the postoperative period. Since 1953 it has practically replaced thoracoplasty as a means of achieving definitive permanent collapse, 21 patients having this operation in less than 18 months, whereas in the same period, only three patients had definitive thoracoplasty (Chart 6). The preliminary results on this group of 21 patients are encouraging. One died of a nontuberculous lesion (perforated peptic ulcer), and two have had resection because the cavity did not close. In both the latter patients the disease was inactive at last report. In four patients the sputum remained positive for tubercle bacilli after plombage and at the time of this report were either waiting for resection or were considered prohibitive risks for resection. Fourteen patients reached "inactive" status after plombage. None of the 20 living patients were any worse for having had plombage. No complications attributable to infection occurred and the spheres were not removed unless resection was performed.

Resection

Pulmonary resection (Chart 7), which was considered far too risky except in practically hopeless situations a decade ago, has now become widely used as an elective procedure in many types of pulmonary tuberculosis. The protection afforded by the antibiotic drugs against postoperative spread, and improved techniques such as segmental resection, have brought about great changes not only in the indications for resective surgery but also in results.

During the first six years of the decade here reported upon, poor risk patients at Vaulain Home had lobectomy or pneumonectomy, often without drug protection. The mortality rate was high, nine early and late deaths from tuberculosis occurring among 22 patients operated upon. After 1950, with the introduction of long term drug therapy and the use of segmental resection, the mortality rate dropped and the number of resections increased. In 1952 32 patients had resection. The indications

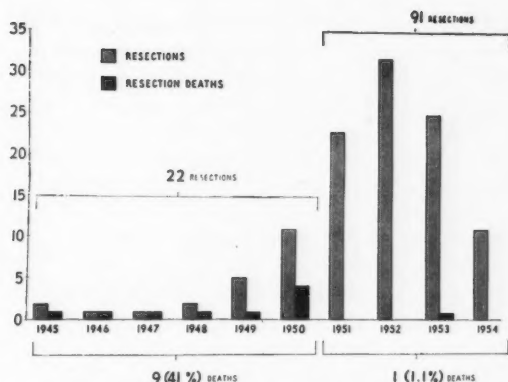


Chart 7.—The number of tuberculosis resections and resection deaths during the decade of 1945 through 1954 at the San Diego County General Hospital.

for resection, which originally included destroyed lobe or lung, bronchostenosis and failure of thoracoplasty were broadened to include residual cavity, blocked cavity, and even residual nodular disease or shrunken segments or lobes, regardless of whether or not there were bacilli in the sputum. Thus, an increasing number of so-called prophylactic resections were performed on patients who were bacteriologically "negative," radiologically "stable" and clinically "inactive."

There have been no reports of adequately followed patients treated with long term drug therapy on the one hand and long term drugs plus resective therapy on the other.³ When such reports are available, should the incidence of reactivation be higher without resection, it could justify a swing toward prophylactic resection. Clinical impressions and a few reports^{1, 2, 6, 7, 8} seem to suggest resection may not have been indicated in some of the elective cases in the present series. At any rate, from the 1952 peak the number of patients who had resection has decreased. Three factors have brought this about: (1) An increasing reluctance of the staff to suggest operations for patients with clinically inactive disease; (2) the introduction of isoniazid and long term multiple drug therapy, which removed certain patients from the list of possible candidates for resection; (3) the greater proportion of older, chronically ill patients in whom resective operation is considered too risky. Thus, the number of so-called elective resections is decreasing compared with salvage resections.

COMPLICATIONS OF SURGICAL TREATMENT

As the decade progressed, relatively fewer complications occurred following operation, owing to the protection afforded by the newer drugs and

the experience gained during the period. At first, drugs were withheld in order that they might be fully useful in event of operation later. As more antituberculosis drugs became available, always one drug was withheld in order that it would be fully effective for use after a surgical procedure. However, as time went on, it appeared that more could be gained by giving multiple drugs initially, regardless of the possibility of future operation. It was reasoned that there was a factor which was not taken into consideration in reports of various series^{4, 5} that seemed to indicate that the complication rate after operation was higher if previous drug therapy had been used, implying the development of drug resistance. It was felt that actually the patients who had had drug therapy were also the poorer risk patients—that they had been given drugs, indeed, for that very reason, and that while it appeared as if the complications were due to drug resistance, actually it may have been that there was a subtle “selection” of poorer risk patients. Hence, with the variety of drugs now available, the possibility that operation may become necessary later is not given a great deal of weight when chemotherapy is decided upon.

Spreads or Reactivations

Spreads or reactivations, which were common following permanent collapse procedures before the advent of specific drugs, are now rare. In fact, late reactivation occurred in one of 21 patients who had plombage after 1951 and in two of 30 patients who had thoracoplasty, neither of whom received isoniazid until after the spread occurred. Before 1951, of 18 patients who survived resection and the immediate postoperative weeks, five had reactivation or spread. Since 1951, of 90 patients undergoing resection, two had spread shortly after operation and five had late spread or reactivation necessitating rehospitalization. Only one of these seven patients died, and in that case death occurred after secondary resection. Only one of the seven patients with reactivation had received long term postoperative chemotherapy, and this did not include isoniazid. None of the patients with reactivation received isoniazid until after the reactivation occurred.

Empyema

Before 1951, empyema occurred in five of 18 patients surviving the immediate postresection weeks. After 1951, this complication developed in four of 90 patients who had resection. Again, the decrease in this complication illustrates more ex-

perience and the great protection of the antituberculosis drugs.

Mortality

Prior to 1951 data were not kept on the death of patients undergoing thoracoplasty, but since 1951 four of 30 patients who had the operation have died, but none as a result of thoracoplasty. One died after secondary resection, the other three from nontuberculous causes. One death (of nontuberculous cause) occurred in 21 patients who had plombage. Nine of 22 patients who had resection before 1951 died of tuberculosis, one of them a year after resection and another four years after operation. After 1951 one patient of 90 who had resection died undergoing secondary resection. Two others have died of nontuberculous causes (Chart 7).

Several factors, other than the increased use of antibiotics, have brought about the decline in surgical mortality and morbidity. One of these is the increased awareness of the importance of operating on patients with stable disease. Also a factor is the increased skill in using the techniques of segmental resection, local excision and wedge resection (the latter very seldom). Simultaneous thoracoplasty and resection has been little used (four patients) because of the increased morbidity with it in the author's experience. Thoracoplasty with intubation has been used in patients in whom residual air pockets developed following resection. This has usually been performed ten days to two weeks after resection and has been done by opening through a rib bed into the air pocket and inserting the tube in such a way that it does not cross the thoracoplasty wound space. This technique has promoted the closure of air pockets quickly without the formation of empyema.

Pneumoperitoneum before and for several months after resection has been used to promote expansion of the unresected lung tissue. Its use has perhaps aided in preventing residual air pockets. The prone position during operation has been used in all poor risk patients and in patients with excessive secretions. Leaving long anterior rib stumps, except of first and second ribs, in definitive and postresection thoracoplasty, has materially reduced paradoxical motion and loss of function postoperatively. The use of as little sedation as is compatible with comfort has made for a smoother and more rapid convalescence.

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ACKNOWLEDGMENT

The author is indebted to Miss Elsa Mikkelsen of the San Diego County Tuberculosis and Health Association for designing the charts, and to Dr. Emerson C. Savage for the data from which the charts are derived, as well as for help in writing this paper.

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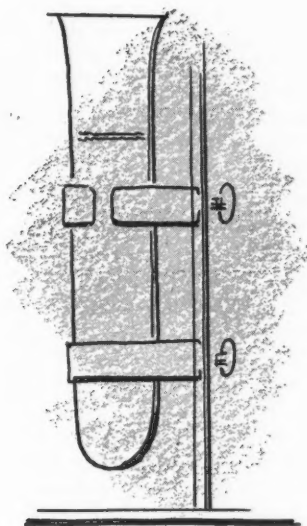
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The Pharmacological Treatment of Headache

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HEADACHE IS A SYMPTOM which may be associated with a variety of clinical conditions whether the underlying disorder be organic, psychologic or psychophysiologic. The appraisal of the results of any method of therapy in patients with chronic headache is extremely difficult, for the major criterion of effect, relief of pain, is subject to many variable factors.

Furthermore, a symptom related to the head is frequently associated with profound anxiety which is due not only to the underlying emotional conflicts responsible for the headache but the threat of the symptom itself. For headache may represent many things to the patient, among which are fear of loss of mind, of disorder of the brain or of impairment of intellectual capacity.

Reading the literature on treatment of chronic headache, a physician is confronted with reports of a consistently high degree of therapeutic success obtained with a variety of remedies. The success of each of the numerous remedies is attributed to the fact that it corrects some hypothesized defect. Among these are reports by certain allergists that over 80 per cent of the patients treated are cured or considerably improved. Ophthalmologists have stated that correction of refractive errors has resulted in considerable improvement in 90 per cent of the patients; endocrinologists note excellent results with various treatments; and reports from orthopedists have indicated successful management of migraine by the use of cervical traction in 85 per cent of cases. Certain psychoanalysts report successful therapy in all cases. Reports by internists claim almost equal success with thiamine chloride, calcium, potassium, histamine desensitization, use of antihistamine, sympatholytics, drugs, sedation, etc. The good results obtained by the primary investigators can seldom be duplicated by others.

With such a diversity of opinions and reports in therapy by the various disciplines, evaluation of pharmacotherapy becomes even more complicated. It is obvious that relative alleviation of symptoms is difficult to ascertain, not only from patient to patient, but also in the same patient during different periods of observation. These differences are empha-

• Often in the treatment of chronic headache, both physical and emotional factors are entailed. Therefore, the results of therapy are limited by the potentialities of the patient in therapy, the pharmacologic actions of the medications used, and the physician's interest and orientation toward the problem. The treatment of choice is generally a combination of psychotherapy and drug therapy. Results in a large series of tests with these types of headaches indicate the effectiveness of treatment is greatly influenced by the patient's psychological reaction to the treatment situation in general and in particular to having received a remedy from the physician. Patients with migraine did not respond to placebos as well as did patients with tension headache, post-traumatic headache and headache associated with hypertension.

sized by reports in the literature which, in some cases, show similar medication yielding completely opposite results, while in others the first glowing therapeutic success diminished to a feeble flicker in later studies.

In the majority of headache problems, the most effective treatment is to relieve the underlying cause. While the use of drugs, in some cases, may not solve the basic therapeutic problem, the importance of drugs in the treatment of headache cannot be minimized. In pharmacologic treatment, attempt is made to do one or more of the following: (1) Raise the pain threshold, (2) interrupt the mechanism producing pain, (3) reduce the emotional tension and anxiety associated with the pain.

In pharmacotherapy the efficiency of any drug does not depend upon its pharmacologic action alone.³ Dosage, timing, mode of administration, tolerance, influence of pathological states, cumulative action and individual idiosyncrasy of the patient are factors of great importance. Furthermore, the efficiency depends greatly upon the patient-physician relationship, which includes, among other things, the attitude of the physician toward the medicine given (positive or negative) and the length and frequency of interviews with the patient. The author believes that patients' reactions to drugs not only depend upon the drug's effect on the underlying disorder responsible for the headache, but also upon the degree of incapacity, constitutional makeup of the patient, duration of symptoms, age of individual, and psychological setting of the therapeutic regimen

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Submitted October 31, 1955.

and status of the patient. What the taking of medication symbolizes to the patient is also a contributory factor in treatment. Is the taking of medication a sign to the patient of weakness, of receiving omnipotent mystical power, punishment or aggression, love and affection? All these factors must be given serious consideration in the clinical usage of drugs in the treatment of headache.

The number and mass of therapeutic agents recommended for relief of headache indicates that there is no one specific form of therapy. Poor results with an agent which has been reported to be effective may indicate that the drug itself is unsatisfactory or that it is being improperly used. From the author's observations, it would appear that the most common causes of therapeutic failures are incorrect diagnosis, inappropriate, inadequate or improper administration of medication, inflexibility of therapeutic regimen and variables in the patient's emotional life.

METHOD

The author knows of no completely accurate method of clinical testing of drugs for headache therapy. The best method of drug evaluation would seem to be the use of the double blind technique in which all agents tested are employed in all subjects. Whenever possible, all "placebo-fast"* patients should be eliminated from the study. In all cases attempt should be made to test more than two agents, which minimizes the chance of placebo detection. Without these techniques, a study of hundreds of cases over a number of years is likely to yield inaccurate results. The trained observer has not proven as valuable a subject as the untrained.¹ The highly trained observer tends to be biased, having an interest in the outcome, whether scientific, pecuniary or emotional. Of course, learning can occur with any subject, but the results are more weighted with the experienced group.

Concurrent observations of the life situations and emotional reactions of the patient and, when possible, of the physician, are most important for critical appraisal of the specific value of the drug being investigated.

Appraisal of Drugs in Specific Headache Entities

The present discussion will be limited to some of the author's past studies on headaches associated primarily with an emotional disturbance (tension headache), cranial trauma (post-traumatic headache), migraine and hypertension.

Since the effectiveness of the various medicaments was said to vary in these specific groups, it is important to define the diagnostic categories used.

*It is normal to respond to placebo effects at times. Patients who almost always or almost never undergo placebo responses have personality patterns which depart from what may be considered the norm.

Differential Diagnosis

1. TENSION HEADACHE:

(a) *Clinical features.* Tension headache occurs in relation to constant or periodic emotional conflict, of which the patients are usually partially aware.⁴ They have no prodromata, are usually bilateral, occipital or frontal, and may be accompanied by a variety of associated signs, including anxiety and nausea. Frequency and duration are variable.

(b) *Mechanisms.* The mechanism by which cranial structures give rise to headache in patients with psychic distress may operate at two levels, each applicable to a different group of psychogenic headaches.

In one group (tension headache) the mental conflict may stimulate the sympathetic or autonomic nervous system with change in the caliber of blood vessels or stimulation of the somatic motor system with contraction of skeletal muscles, particularly those of the neck.

In another group (conversion headache) the symptom represents a specific unconscious symbolic meaning, and conversion mechanisms are prevalent. Headache of this type cannot be distinguished from tension headache by clinical description alone.

In tension headaches muscular or vascular mechanisms may act independently or concomitantly. With muscle tension, sustained contraction of the skeletal muscles of the head and neck causes pain or dysesthesia in the neck and scalp. Associated with these muscular spasms may be ischemia which could be a contributory or primary factor in the induction of pain. It has also been hypothesized that excessive concentration of potassium in muscle from ischemia or sustained contraction stimulates the chemoreceptors in the tissues. Another factor responsible for the head pain may be a central spread of the excitatory effect of noxious stimulation of the soft tissues of the neck. This spread of pain is carried by the upper cervical nerves and may produce painful sensations in the forehead and face.

2. POST-TRAUMATIC HEADACHE:

One of the most frequent sequelae to injury of the head is post-traumatic headache. This occurs in approximately 60 per cent of patients who have had head injuries.² Post-traumatic headache resembles tension headache. The headache is usually referred to the side or part of the head which the patient associates with the injury. The physiologic mechanisms which are presumably involved in the production of post-traumatic headaches are distention of cranial blood vessels, sustained contraction of the skeletal muscles of the head and neck, and scarring of the extracranial soft tissues.

The incidence of prolonged headache in patients following head injury was associated with neurotic symptoms prior to injury, with symptoms of marked immediate emotional reaction to the injury, and with complicating environmental factors which might be presumed to cause the usual emotional stress.

3. MIGRAINE:

(a) *Clinical features.* Migraine may be defined as that form of headache which is characteristically paroxysmal, periodic, unilateral and throbbing. The headache occurs against a background of relative well-being, is often preceded by visual or psychological disturbances, and is usually associated with vomiting and irritability.

(b) *Physiological mechanisms.* The following physiological changes occur in an attack of migraine:^{8,9} An initial vasoconstriction of certain intracranial branches of the internal carotid artery produces visual and possibly other preheadache phenomena before the onset of the headache. This prodromal period is followed by dilation and distention of cranial arteries, primarily in the area of distribution of the external carotid artery. Stimulation of pain-sensitive nerves in and around the dilated vessels by the increased amplitude of pulsation is the presumed cause of the headache. Persistent dilation results in a rigid, pipe-like state of the vessels. The pain at this stage is a steady ache, replacing the earlier throbbing, pulsation type. During or following this stage, there is contraction of the neck muscles, and "muscle-contraction pain" develops. This spasm of the muscles is a reaction to the initial pain and may outlast it. The initial phase of the headache is due to stimulation of pain endings which lie in or near the walls of the intracranial arteries, whereas the latter, or "muscle pain," is probably the result of either direct stimulation of nerve endings or ischemia of the muscles. Although in migraine the immediate cause of pain is associated with dilation of cranial arteries, it is evident that dilation of blood vessels alone is not sufficient to produce headache. Other dynamic or chemical factors as yet not clearly delineated must contribute.

A small but important group of patients observed by the author with the clinical features of frequent migraine headaches turned out to be schizophrenic. These patients had many pseudoneurotic symptoms which were associated with a feeling of catastrophe, oddities of behavior, a gradual withdrawal from reality and descriptions of situations which are nebulous and changeable. Such persons seldom respond to psychotherapy or medication for symptomatic treatment of an attack. The obvious schizophrenic behavior usually occurs much later. In many of these patients the nature of the mechanism is not peripheral and remains obscure. Recognition of this

problem is important to avoid needless routine therapy for the patient and frustration for the physician, and to insure adequate early treatment of the schizophrenia.

4. HEADACHES ASSOCIATED WITH HYPERTENSION:

(a) *Clinical features.* The headache of arterial hypertension is usually a dull, throbbing, deep ache. It is aggravated by strain, stooping and emotional tension. This headache may be generalized or confined to the front or back of the head. Although usually bilateral, it may resemble migraine by periodicity and by being confined to one side of the head. It often appears upon the awakening of the patient and may improve as he moves about. Nausea and vomiting are infrequently noted. Another variety of headache occurring with hypertension is a suboccipital tightness and rigidity which may encircle the head.

(b) *Physiological mechanisms.* The pathogenesis of headache in essential hypertension is obscure. The degree of headache is not proportional to increased blood pressure. The headache may be present when the blood pressure is low as well as high. It is postulated that variation in the contractile state of the cranial arteries is the cause of the headache, and that the elevated blood pressure is only an accessory factor. Experimental administration of ergotamine tartrate usually abolishes the headache, which would indicate that the mechanism of pain production may be similar to that in migraine. Headache of this kind is not due to increased intracranial pressure since this pressure is normal, nor will elevating the pressure experimentally produce the pain. There is no relationship to impairment of renal function in headaches associated with hypertension. When the blood pressure is lowered by therapeutic measures, such as sodium restriction or antipressor drugs, the headache disappears.

EVALUATION OF AGENTS USED IN TREATMENT

In the past ten years the author has evaluated a number of agents in the treatment of headache. Following is a discussion of the results of three separate studies:

1. The effectiveness of drug therapy in the treatment of tension and post-traumatic headache is influenced by many factors. In a series of over five hundred patients the effectiveness of the medication depended to some extent on the physician prescribing the medication, the time he spent with the patient, and the frequency with which the patient was seen by him.⁵ It was noted that in many cases patients would maintain a state of improvement if they were seen at weekly intervals, but would have recurrence of headaches if they were seen at monthly intervals instead.

In addition, the factors of disability compensation and litigation played a part in many cases of post-traumatic headache.

Fifty to sixty per cent of the patients with psychogenic and post-traumatic headache responded favorably to almost any medication given to them. The drugs used included analgesics, vasoconstrictors, vasodilators, hormones combined with vitamins, placebos, and parenterally administered isotonic sodium chloride solution. The analgesics, and some of the oral placebos were taken only at the time of the headache, while the hormone-vitamin combinations and isotonic sodium chloride solutions were given by injection at regular intervals. The effect of medication given by injection in cases of psychogenic illness is too well known to require further discussion here. In addition, several of the patients receiving the combinations of hormones and vitamins reported a feeling of well-being that undoubtedly played some part in their improvement. The similarity of response of pain with the various medications in tension and post-traumatic headache again emphasizes the close relationship between these two types of headache.

The best results in each group of patients were obtained by the use of analgesics. The other drugs gave no better results than those obtained by the use of inactive substances.

2. In a study with 2,000 patients with migraine or tension headache the following results were noted.⁶ The most effective symptomatic treatment of migraine was oral or rectal administration of ergotamine tartrate and caffeine (Cafergot®). Rectal use of Cafergot proved empirically to be most efficacious especially when oral medication could not be retained. It is likely that rectal medication has the advantage of being absorbed more directly into the systemic circulation without having to penetrate the hepatic and gastric barriers. Hence it is postulated that this action is quicker with less side effects than with oral administration. This requires further investigation. The psychological connotation of taking medication via rectum must also be given consideration. Fifty-six agents were tested in this study and approximately 80 per cent of the patients received symptomatic relief by early and adequate administration of some form of ergotamine and caffeine whereas only 25 per cent had the same response to placebos. In cases of tension headache, the treatment of choice was a combination of an analgesic and sedative. Fifty different combinations of drugs were used in this study. Sixty-five per cent of the patients studied received relief symptomatically by use of analgesic-sedative combination. The placebo response in this group was close to 50 per cent.

This study indicated that, except in a few isolated cases, there are no known drugs available which are

helpful prophylactically in the treatment of migraine. In an occasional case, the allergic, hormonal or metabolic factor, when adequately controlled, may prevent the onset of an attack of migraine. However, in a great majority of patients who have migraine, control of the psychic and stress factors is the most successful method of treatment.

As in migraine, there is no good prolonged medical treatment for tension headaches, although the use of sedation and some of the newer medicaments, such as Reserpine and chlorpromazine, may prove mildly successful. In general, both of these conditions require psychotherapy for adequate control, as this is the only method in which the patient's emotional conflicts can be resolved.

3. In a recent study⁷ in which rauwolfia was used in a series of 220 patients with headaches that were diagnostically divided into migraine, tension and headaches associated with hypertension, it was found that in patients with migraine, 38 per cent had a reduction in frequency of these headaches; in patients with tension headaches, 75 per cent had improvement in headache status; and in patients with headache associated with hypertension, 80 per cent showed reduction in frequency of headache. However, all these data must be considered in the light of placebo experience in the same series, which indicated a favorable result in over one-half of the migraine and tension cases, and two-thirds of the cases of headache associated with hypertension.

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Neomycin in Urinary Tract Infections

A Clinical Evaluation

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NEOMYCIN IS AN ANTIBIOTIC, water-soluble, polybasic compound elaborated by a strain of *Streptomyces fradiae*.⁶ It is very active against many Gram-negative bacilli as well as some Gram-positive bacteria, and is particularly useful in urinary tract infections where the organisms are resistant to other antibiotic and chemotherapeutic agents.

A wide range of bacteria is susceptible to neomycin *in vitro* and *in vivo*. *Aerobacter aerogenes* and *Escherichia coli* are among the very sensitive organisms. Some strains of *Pseudomonas aeruginosa* and *Proteus vulgaris* are sensitive to the drug while others are more resistant.² It is also effective against certain Gram-positive organisms such as *Micrococcus pyogenes* and an occasional streptococcus. Neomycin is bactericidal against many organisms and is bacteriostatic against a few (*Ps. aeruginosa* and *B. proteus*). In many instances, organisms that are resistant to streptomycin will be sensitive to neomycin. This includes the tubercle bacillus. Resistance to neomycin can develop rapidly in some organisms (*Ps. aeruginosa* and *B. proteus*) but the very susceptible Gram-negative organisms and tubercle bacilli develop resistance to it more slowly than to streptomycin.² Although streptomycin-resistant strains are sensitive to neomycin, strains that have developed resistance to neomycin also demonstrate increased resistance to streptomycin. Neomycin and the tetracycline group, however, act independently in regard to resistant organisms.

Neomycin is rapidly absorbed after intramuscular injection and is excreted by the kidneys in high concentrations. Although it is demonstrable in the blood stream within a few minutes after injection, urinary excretion continues for 24 hours after the last dose.² When it is given orally, there is very little absorption and Pulaski found that only 3 per cent was excreted in the urine, the rest being recovered in the feces in active form.²

Limitations of the use of neomycin are due to the nephrotoxic and neurotoxic factors inherent in the antibiotic. The effect on the kidneys may cause enough irritation to produce transient mild proteinuria, fine granular casts and, occasionally, mild

• Neomycin was effective in treating 31 cases of severe Gram-negative bacillary urinary tract infections sensitive to neomycin and resistant to other agents. The recommended dosage schedule of 0.5 gm. every 12 hours for five days was demonstrated to be relatively safe. However, close watch should be maintained for signs of nephrotoxicity and ototoxicity.

elevation of the nonprotein nitrogen in the blood. The neurotoxic effects may be those of disturbances of hearing and are more likely to occur when poor renal function interferes with proper elimination of the drug or when it is used in large doses and for long periods.⁵

This report is concerned with the therapeutic effectiveness of neomycin and the absence of serious toxicity when given in a low dosage schedule for a limited duration of treatment. In a series of 31 patients who received 1 gm. or less of neomycin daily for a total of five days or less, no serious untoward effects occurred and the therapeutic results were such as to warrant its more widespread use. Nesbit and co-workers reported a previous series with similar findings.¹

CLINICAL STUDY

Neomycin therapy was evaluated in 31 cases of severe urinary tract infection (Table 1). All the patients had previous chemotherapeutic or antibiotic trials without success. *In vivo* and *in vitro* resistance was present or had developed generally to all agents other than neomycin (penicillin, streptomycin, tetracycline, chloramphenicol, furadantin, polymyxin, erythrocine, sulfonamides). In many instances clinical response to mandelamine was likewise poor. Many of this group of patients had obstructive urinary tract lesions and would not ordinarily be considered likely candidates for eradication of infection by antibiotics. In addition, varying amounts of renal damage were present in some patients prior to treatment with neomycin.

Urine cultures and sensitivity studies were largely done by the plate method. One tenth milliliter of urine was spread over a blood-agar plate in which the concentration of neomycin was 10 micrograms

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Submitted December 23, 1955.

per milliliter. After 24 and 48 hours, the absence of colonies was interpreted as indicating that organisms in the urine were sensitive to the drug, the presence of colonies as indicating resistant organisms.³ In some cases the test was done by the tube dilution method. Sensitivity to neomycin varied: From 2 to 30 mcgm. per milliliter was needed, the organisms being sensitive to 10 mcgm. per milliliter in vitro in the average case. Six groups of bacteria in both pure and mixed infections were treated—*E. coli*, *B. proteus*, *Ps. aeruginosa*, *A. aerogenes*, paracolon group and *Enterococcus*.

The usual dosage schedule for adult patients was 0.5 gm. of neomycin every 12 hours for an average total of eight doses. One patient was treated for one week, and 15 were treated for less than eight doses. Treatment was shortened in the latter group because of rapid therapeutic response or initially impaired renal function, but not because of developing toxicity. An attempt was made to reduce the dosage of neomycin still further and yet obtain sterilization of the urinary tract. In five cases of long-standing, chronic, deep-seated infection the urine was rendered sterile on a dosage of 0.25 gm. every 12 hours for eight doses. Three patients were children. Neomycin sulfate (Mycifradin, Upjohn) was used throughout.

Daily complete urinalysis was done on every case and the nonprotein nitrogen, serum creatinine or phenosulfonphthalein excretion were measured before and immediately after therapy. Some patients were observed from time to time for as much as a year after treatment and no latent toxicity which did not appear during treatment was noted. No audiometric tests were done but gross auditory disturbances were carefully watched for. Urine cultures were done before treatment, during treatment, immediately following cessation of therapy and then at varying intervals for as long as a year. On subsequent follow-up, if there was any indication of recurrent infection either by symptoms or stained smear of the urine, cultures were done. For the most part, patients were followed for at least two to six months. Three patients were treated on an outpatient basis. Because previous laboratory studies had already provided adequate data on blood and urinary levels of neomycin, these studies were not done in the present series.

RESULTS

Of the 31 patients treated, none had gross neurotoxic effects from neomycin. In five cases transient mild proteinuria developed and there were a few fine granular casts. Treatment was not discontinued because of these developments and the urine returned to normal either during or immediately after treatment. None of the four patients with impaired renal

function had any increased impairment, and only two showed slight renal toxicity from neomycin.

Twenty of the patients were cured or had permanent improvement. One patient died of postoperative complications, but he had had dramatic response to neomycin, with rapid sterilization of the urine and no apparent toxic effect from the drug. There were two complete failures in patients with pronounced obstructing lesions. Three others showed significant clinical improvement but complete sterilization of the urine was not accomplished. Five patients had temporary remission lasting from eight days to two months. Only one of these had nonobstructive urinary tract disease. The others all had severe obstructive uropathic conditions and debilitating chronic disease other than infection.

In most of the patients with poor results there was mixed infection with one or more of the organisms resistant to neomycin. In four such cases, subsequent cultures revealed the same organism which had become resistant to neomycin. One patient had immediate reinfection with a new organism—*Ps. aeruginosa*. Three others had good clinical response immediately but later had infection with *Ps. aeruginosa* or *Proteus*.

There were no episodes of diarrhea, itching, dizziness, headache, sweating, nausea or other symptoms often associated with the more common antibiotics.

DISCUSSION

It is recommended that neomycin therapy be reserved for patients with severe Gram-negative neomycin-sensitive infections that do not respond to other less potentially toxic agents.² For this group of patients, neomycin appears to be a valuable addition to the urologic armamentarium of antibiotics. Its therapeutic effectiveness permits its use in low doses over a short period of time so that the potential hazards of toxicity are minimized. Indeed, some of the patients in the present series were females with long standing chronic cystitis. In these cases, good results were obtained with only 0.25 gm. every 12 hours for as few as four or six doses. In the average adult with normal renal function, a dose of 0.5 gm. every 12 hours for five days is relatively safe and may be given to an ambulatory patient. The patient should be observed for nephrotoxicity by daily urinalysis for proteinuria, casts and renal cells. Any nephrotoxic changes observed during this dosage schedule appear to be completely reversible. In the present series there were no cases in which there was detectable ototoxic effect. However, it must be emphasized that neomycin is a toxic drug and although there was no serious toxicity observed with the dosage schedule described, permanent deafness has resulted in patients treated with a neomycin

TABLE 1.—Clinical and Laboratory Data on 31 Cases of Urinary Tract Infections Treated with Neomycin

Diagnosis	Age Sex	Initial Renal Function	Initial Culture Sensitivity Mgm./ml.	Dosage	Previous Therapy	Culture After Therapy	Toxicity	Results
1. Severe chronic pyelonephritis. Solitary kidney.	25 M	Impaired: BUN 46.7 mgm. %, Serum creatinine 2.5 mgm. %, PSP 32% 2 hr.	E. coli: 2 A. aerogenes (also sensitive to tetracycline: 10)	0.5 gm. q 12 hr. × 2 gm. per day of tetracycline for 1 wk. Total: 7 gm.	Usual plus streptomycin	Sterile	None	Marked improvement. Urine negative, sterile, with no recurrent pyuria. 9 mo. follow-up.
2. Chronic cystitis, persistent pyuria. Symptoms 5 yr.	45 F	Normal	A. aerogenes: 2	0.5 gm. q 12 hr. × 10 Total: 5 gm.	Usual plus streptomycin	Sterile	None	Persistent relief from symptoms. Urine negative, sterile. 4 mo. follow-up.
3. Bilateral hydronephrosis, hydronephrosis. Severe, acute and chronic bilateral pyelonephritis. Temp. 40° C. 59 lb. PSP 30% 2 hr.	8 M	Impaired: BUN 52	Ps. aeruginosa A. aerogenes: 30	200 mgm. q 12 hr. × 6 Total: 1.2 gm.	Usual plus streptomycin	Sterile	None	Afebrile 6 hr. after first dose. Urine sterile in 48 hr. 4 mo. follow-up.
4. Chronic cystitis, 4 yr., persistent pyuria, severe symptoms. (Had remission during furazolidin therapy but couldn't tolerate drug.)	59 F	Normal	B. proteus: 30	0.5 gm. q 12 hr. × 10 Total: 5 gm.	Usual	Sterile	None	Prompt remission within 48 hr. Culture sterile, asymptomatic. Relapse after 2 mo. Organism now resistant.
5. Severe recurrent acute prostatitis. Temp. 39.8° C. No residual urine.	45 M	Normal	A. aerogenes: 10	0.5 gm. q 12 hr. × 10 Total: 5 gm.	Usual	Sterile	None	Afebrile within 24 hr., urine sterile in 48 hr. 6 mo. follow-up.
6. Congenital bladder neck obstruction, bilateral ureterovesical obstruction. Bilateral hydronephrosis and hydronephrosis.	4 M	Impaired: Urea 60 mgm. %	Ps. aeruginosa Paracolon: <10	0.075 gm. q 12 hr. × 8, Polymyxin 0.020 gm. q 12 hr., Strep. 0.25 gm. q 12 hr.	All types except neomycin, polymyxin	None	Life saving treatment, afebrile within 48 hr. after 1st dose. Required 2 courses of treatment. Ten days apart for septicemia following catheterization.
7. Postoperative cesarean section with pelvic hematoma, pyelonephritis acute.	34 F	Normal	E. coli: <10	0.25 gm. q 12 hr. × 8 Total: 2.0 gm.	Usual plus streptomycin	Sterile	Granular casts	Afebrile 24 hr. after cessation of therapy. Follow-up 1 mo.
8. Postoperative radical panhysterectomy for carcinoma cervix, stricture right ureter with hydronephrosis and chronic urinary tract infection.	28 F	Normal	E. coli: <10	0.25 gm. q 12 hr. × 8 Total: 2.0 gm.	Sulfonamides	Sterile	None	Afebrile within 6 hr. after initial dosage.
9. Recurrent carcinoma, Bartholin duct. Chronic cystitis.	56 F	Normal	B. proteus, Ps. aeruginosa: <10	0.125 gm. q 12 d. × 5 Total: 0.62 gm.	Usual	Sterile	None	Cured. 14 days follow-up.
10. Sarcoma uterus, vesicocutaneous fistula. Chronic urinary tract infection. Hydronephrosis.	44 F	Impaired: Urea 52 mgm. %	A. aerogenes E. coli: <10	0.25 gm. q 12 hr. × 8 Total: 2.0 gm.	Sulfonamides	Sterile	None	Symptomatic improvement. Slight remission 8 days.
11. Chronic urinary tract infection. Diabetes.	51 F	Normal	A. aerogenes: <10	0.25 gm. q 12 hr. × 4 Total: 1.0 gm.	Usual	Sterile	None	Improved. Culture sterile at 12 days follow-up.
12. Cancer lung, BPH, Urethral stricture with indwelling catheter.	48 M	Normal	Paracolon Ps. aeruginosa A. aerogenes: <10	0.5 gm. q 12 hr. × 4 Total: 2.0 gm.	Usual plus streptomycin	Ps. aeruginosa	None	No clinical improvement except a decrease in pyuria.
13. Pyelonephritis, postoperative ureterectomy. No indwelling catheters.	80 M	Normal	A. aerogenes: <10	0.5 gm. q 12 hr. × 8 Total: 4 gm.	Usual	Sterile	None	Afebrile 24 hr. after first dosage. Marked relief of symptoms.
14. Postoperative TUR prostate, bilateral ureteral-vesical obstruction, indwelling urethral catheter.	69 M	Normal	B. proteus E. coli: <10	0.5 gm. q 8 hr. × 8 Total: 6 gm.	Usual plus streptomycin	Ps. aeruginosa	None	Temporary improvement, afebrile 3 days. Prompt reinsertion with Ps. aeruginosa.
15. Postoperative colectomy, acute renal failure: urinary tract infection in diuretic phase.	57 M	Impaired: Creatinine 2.7 mgm. %, urea 131 mgm. %	E. coli Paracolon: <10	0.25 gm. q 12 hr. × 4 Total: 1 gm.	Usual plus streptomycin	Sterile	Granular casts 1+ protein	Temporary improvement, reinsertion 10 days after neomycin therapy with B. proteus, E. coli and Paracolon.

TABLE 1.—(continued)

Diagnosis	Age Sex	Initial Renal Function	Initial Culture Sensitivity Ingm./ml.	Dosage	Previous Therapy	Culture After Therapy	Toxicity	Results
16. Postoperative abdominal-perineal resection. Urinary tract infection.	55 M	Normal	B. proteus A. aerogenes Enterococci Ps. aeruginosa	0.5 gm. q 12 hr. × 8 Total: 4.0 gm.	Usual plus streptomycin	(Few colonies) Ps. aeruginosa	None	Symptomatic improvement, afebrile within 12 hr. after initial dosage.
17. Postoperative laminectomy for spinal fusion. Urinary tract infection.	55 F	Normal	A. aerogenes: <10	0.5 gm. q 12 hr. × 4 Total: 2.0 gm.	Usual	Sterile	Casts, 1+ protein for 1 day	Afebrile 8 hr. after first dosage. No recurrence 1 yr. follow-up.
18. Meningocele with hypotonic bladder and incontinence.	16 M	Normal	Paracolon: <10	0.5 gm. q 8 hr. × 9 Total: 7.0 gm.	Usual	Sterile	None	Temporary improvement. Recurrence in 2 mo.
19. Agnecis right kidney, bladder neck obstruction, indwelling catheter.	25 M	Normal	E. coli Paracolon: <10	0.5 gm. q 12 hr. × 7 Total: 3.5 gm.	Usual plus streptomycin	Sterile	None	Afebrile 12 hr. after initial dose, with symptomatic improvement. Late reinfection with B. proteus, Ps. aeruginosa.
20. Spinal cord tumor with cord bladder, indwelling catheter.	54 F	Normal	Paracolon: <10	0.5 gm. q 12 hr. × 3 Total: 1.5 gm.	Usual plus streptomycin	Sterile	None	Cured. 4 mo. follow-up.
21. Hodgkin's disease. Pylonephritis, chronic. Solitary kidney.	31 M	Impaired: Urea 60 mgm. %	E. coli: <10	0.5 gm. q 12 hr. × 4 Total: 2.0 gm.	Usual	Sterile	Granular casts 1+ protein	Remission after 12 days.
22. Postoperative TUR prostate.	71 M	Normal	Paracolon: <10	0.5 gm. q 12 hr. × 4 0.25 gm. q 12 hr. × 2 0.125 gm. q 12 hr. × 8 Total: 3.5 gm.	Usual	Sterile	None	Afebrile within 12 hr. after initial dosage. Complete symptomatic relief, although reinfection with Ps. aeruginosa in 8 days.
23. Carcinoma prostate with metastases. Indwelling catheter.	71 M	Normal	Ps. aeruginosa Paracolon, E. coli Enterococci	0.5 gm. q 12 hr. × 9 Total: 4.5 gm.	Sulfonamides	Ps. aeruginosa	Granular casts 1+ protein	No change except for marked decrease in pyuria.
24. Ureterovesical stricture.	5 M 45 lb.	Normal	B. proteus: <10	0.25 gm. q 12 hr. × 3 Total: 0.75 gm.	Usual plus streptomycin	Sterile	None	Cured. 1 yr. follow-up.
25. BPH, indwelling catheter.	66 M	Normal	Paracolon Ps. aeruginosa: <10	0.5 gm. q 12 hr. × 3 Total: 1.5 gm.	Usual	Ps. aeruginosa	None	Afebrile 12 hr. following initial dose. Sterile culture after removal of catheter.
26. Horseshoe kidney, hydronephrosis, prostatic obstruction with urethral catheter.	23 M	Normal	A. aerogenes: <10	0.5 gm. q 12 hr. × 6 Total: 3.0 gm.	Usual	Sterile	None	Afebrile 24 hr. following initial dose. Reinfection after 1 mo.
27. Postoperative TUR prostate, pyelonephritis.	68 M	Normal	E. coli: <10	0.5 gm. q 12 hr. × 6 Total: 3.0 gm.	Usual plus streptomycin	Sterile	None	Prompt symptomatic response. Afebrile 18 hr. after first dosage. Late reinfection B. proteus in 3 mo.
28. Postoperative TUR prostate, urethral stricture, with indwelling catheter, pyelonephritis.	67 M	Normal	E. coli: <10	0.5 gm. q 12 hr. × 3 Total: 1.5 gm.	Usual	Sterile	None	No recurrence after 20 days.
29. Diabetes, pyelonephritis, acute.	60 F	Normal	A. aerogenes: <10	0.5 gm. q 12 hr. × 10 Total: 5.0 gm.	Usual	Sterile	None	Prompt symptomatic relief. Afebrile 6 hr. after initial dosage. 2 mo. follow-up.
30. Postoperative esophagectomy with esophago-pleural fistula. Urinary tract infection.	69 F	Normal	E. coli: <10	0.5 gm. q 12 hr. × 7 Total: 3.5 gm.	All types except neomycin	Sterile	None	Culture remained sterile until death from postoperative complications.
31. Postoperative arthrodesis hip, cystitis with indwelling catheter.	43 M	Normal	E. coli: <10	0.5 gm. q 12 hr. × 5 Total: 2.5 gm.	Usual	Sterile	None	Afebrile 24 hr. after initial dose. Cured. 2 mo. follow-up.

NOTE: Usual antibiotics include tetracyclines, penicillin, sulfonamides, chloramphenicol.

Abbreviations:
BUN=Blood urea nitrogen.

NPN=Nonprotein nitrogen.
PSP=Phenolsulfonphthalein.

BPH=Benign prostatic hypertrophy.
TUR=Transurethral resection.

dosage schedule slightly heavier than that used in the series here reported upon. Neomycin should therefore be administered only to selected patients.

Even though the therapy failed in 10 of the 31 patients, the results still would actually denote pronounced therapeutic effectiveness. All the patients had severe or chronic urinary tract disease and infection that did not respond to other forms of therapy and they were given neomycin as a "last resort." All but one of the patients in whom neomycin therapy failed had accompanying obstructing lesion with irreversible disease. In general, the *in vitro* sensitivity of bacteria to neomycin in concentrations of less than 10 mcgm. per milliliter would indicate a potentially satisfactory *in vivo* result. There was good correlation between results of testing *in vitro* and the *in vivo* response. In patients with impaired renal function, neomycin therapy need not be withheld if it might be a life-saving measure; however, there should be close watch for both ototoxic and nephrotoxic effects. Therapeutic response is frequently so rapid and striking that only a day or two of treatment may result in dramatic improvement in these patients. In the present small series, patients with impaired renal function tolerated therapy as well as those with normal function.

The authors have been impressed with the frequency of the enhancement of neomycin effect *in vitro* when other antibiotics are added to it. This consideration is even more worthwhile when *in vitro* testing reveals only moderate sensitivity and when seriously impaired renal function would make very low dosage and short duration of neomycin therapy more desirable. Polymyxin was used simultaneously

in one of the cases in this series and tetracycline in another. Both patients had mixed infections.

CONCLUSIONS

Neomycin is a useful antibiotic in urinary tract infections caused by Gram-negative organisms which are neomycin-sensitive and resistant to other agents.

A dosage schedule of 0.5 gm. every 12 hours for ten doses appears to be therapeutically effective and relatively safe in adults with normal renal function.

Patients receiving the drug should be closely followed for potential nephrotoxicity and ototoxicity.

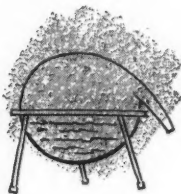
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ACKNOWLEDGMENT

The authors are indebted to Dr. Robert Roantree and Dr. Lowell A. Rantz for help in management of many of the patients in the series here reported upon. Cases 11 to 31 will also be described by them.⁴

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Congenital Aganglionic Megacolon

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THE PRESENT CONCEPT of the cause of congenital aganglionic megacolon (Hirschsprung's disease) is the result of half a century of studies beginning with the pathological reports by Tittel⁶ (1901) and culminating in the widespread acceptance of the experimental and clinical studies of Swenson and co-workers^{3, 4, 5} (1948-1949). This concept assumes the presence of an area of colon (usually rectosigmoid) in which the ganglion cells of the myenteric plexuses are congenitally absent, resulting in a lack of coordinated peristaltic activity. The dilation and hypertrophy of the proximal colon is a compensatory phenomenon. Swenson revived and applied to this problem a procedure consisting of coloproctectomy with reconstruction of the alimentary tract by a "pull-through" (1948) and has since performed over one hundred such operations. Pull-through procedures were first performed in the Los Angeles Children's Hospital in 1949. The first patients included five children with long standing megacolon. Fourteen additional patients were subjected to resection during the subsequent five years.

The clinical material from this pediatric center was studied with emphasis on the following: (a) An evaluation of the pull-through procedure and its modifications in the treatment of megacolon and (b) a study of this disease as it appears in early infancy. The operative cases from 1949 through 1954 form the basis for the former evaluation, (a); and all neonatal cases from 1943 to 1954 were surveyed in the later study (b).

EVALUATION OF PULL-THROUGH PROCEDURE

Operative Clinical Material

Nineteen children with aganglionic megacolon were treated by coloproctectomy and pull-through reconstruction or a similar procedure (total of 23 operations) during the five-year period 1949-1954. The diagnosis was established by pathological examination of the operative specimen in all cases and confirmed by subsequent autopsy in four cases. Fifteen male and four female children were included in the operative group. The age at the time of the first hospitalization for megacolon varied from two days to 15 years (average 2.3 years). The age at the

• Twenty-one pull-through procedures for congenital aganglionic megacolon (Hirschsprung's disease) have been performed at the Los Angeles Children's Hospital since the adoption of the etiological concept of a distal aganglionic segment in 1949. In 14 cases the Swenson procedure as modified by Hiatt was employed, with perineal excision of the colon segment. There were four postoperative deaths and three symptomatic recurrences in this group. Three patients were treated by transabdominal resection of colon and rectum with subsequent pull-through reconstruction (Swenson). Anterior resection (State) was carried out in two cases. Three children with recurrence of symptoms following primary operation were subjected to a secondary pull-through procedure with an eventual successful outcome. The major portion of the postoperative mortality (29 per cent) in this group occurred in infants less than six months of age in whom anastomotic disruption or proximal segment infarction occurred after operation.

A study of 31 cases of congenital aganglionic megacolon in very young infants drew attention to the difficulty of establishing a diagnosis in this age group even at exploratory laparotomy. Among these infants the mortality rate was excessive, regardless of the form of therapy employed. Colostomy appeared to be the indicated surgical procedure if a conservative regimen failed to control intractable colonic obstruction during the first year of life.

time of the definitive operation varied from one month to 15 years (average 3.6 years). In recent years the operation has usually been performed on patients between the ages of two and three years, and no child over the age of five has been operated upon for megacolon in this hospital since 1952.

History and Physical Findings

Constipation was the universal principal symptom. A history of low intestinal obstruction dating from the first six months of life was obtained in all cases. Bowel evacuation problems in the postnatal month were described in 17 children; and approximately 50 per cent of the entire group were said never to have had a spontaneous bowel movement. Children who had defecation without enemata (approximately 50 per cent) usually passed a massive stool one or two times each week, particularly after the first year of life. The sand-like nonfecal character of the stools of these children was unique.

Vomiting occurred during obstructive episodes in

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Submitted October 1, 1955.

TABLE 1.—Congenital Aganglionic Megacolon. Results of Operative Procedures Employed (1949-1954)

Type of Operation	Total No.	Postoperative Deaths	Second Operation Required	Ultimate Result	
				Poor	Good
1. Perineal colon resection (pull-through)....	14	5	3	1	8
2. Abdominal colon resection (pull-through)	3	1	0	0	2
3. Lower anterior resection.....	2	0	1	0	2
Total.....	19	6	4	1	12

eight children. Diarrhea alternated with constipation in five cases, and in four the abdominal distention was so great as to cause respiratory embarrassment. When the home care was energetic—daily effective enemata—the more striking symptoms were usually absent after the first year.

Severe malnutrition with retardation of growth was noted in three children. No definite evidence of malnutrition or retardation of any type could be detected among the remaining patients who survived infancy. Three major associated congenital anomalies (mongolism, patent ductus arteriosus and congenital hydronephrosis) were present in the cases in which autopsy was done. The physical findings associated with congenital aganglionic megacolon were unique only among the older children with low intestinal obstruction in whom the thick-walled, dilated colon could be readily palpated.

Roentgen Studies

Roentgenographic visualization with barium enema in all cases (19 children) showed dilation of the proximal colon with characteristic narrowing in the lower rectosigmoid or upper rectum to the caliber of normal bowel. In two infants this vital diagnostic feature was at first equivocal, although it became definite before the age of one year. The distal extent of the aganglionic segment was incorrectly predicted by barium enema studies in two instances, resulting in incomplete rectal resection. Following a successful pull-through procedure, x-ray studies uniformly showed a return of the remaining colon to normal caliber and configuration. Plain films of the abdomen did not aid in distinguishing congenital aganglionic megacolon from other forms of subacute intestinal obstruction in early infancy. Retention of a mass of barium given as an enema, retained and desiccated, was a major complication in the preoperative preparation of two children.

Operative Findings

At the initial abdominal exploration the extent and degree of colonic dilation was extremely variable. The difficulty in recognizing the disease in early infancy will be discussed in the subsequent section. Following colostomy the bowel returned to normal caliber and appearance when seen at subsequent abdominal exploration (two cases). In the

older infants and children in the present series the conventional dilation from the midtransverse colon to the rectosigmoid was noted in five cases. In addition to the conventional pattern, the ascending colon was dilated in five additional patients. The sigmoid alone was the site of dilation in three children. "Skip" areas of dilation in both right and left colon were noted in one infant. In one the dilation extended into the rectum but not to the anal sphincter.

The average length of colon resected was 18.1 cm. This average included several minimal resections performed early in the series. In later years, resections were between 20 cm. and 30 cm. in length and included the major portion of the descending colon, sigmoid colon, and rectum.

Operative Procedures

Three operative techniques were employed in this series. Swenson's procedure as modified by Hiatt⁵ was used in 14 cases. The rectum and colon were resected from below following complete intussusception of the distal bowel, and the anastomosis was made at the perineum, and inverted. There were four postoperative deaths and three recurrences in this group (Table 1).

In three cases a transabdominal resection of the dilated colon (Swenson) was performed, followed by intussusception of the distal stump and anastomosis at the perineum. One patient died after operation. There were no recurrences.

In two cases a low anterior resection (State)² was performed. In only one of these was a complete left colectomy performed, however. One recurrence occurred; it was successfully treated by a pull-through procedure.

Since 1953, serial "frozen sections" have been taken at the operating table to determine the extent of the aganglionic area. At first both the proximal and distal ends of the proposed segment for resection were examined for the presence of ganglion cells in the myenteric plexuses. Recently the dissection has been carried distally to within several centimeters of the anus (region of the internal sphincter) without regard to the presence of ganglion cells in the rectal wall. There has been no recurrence of obstructive megacolon since the introduction of this technique. All patients with previous

TABLE 2.—Deaths and Major Complications Following Pull-Through Procedures for Congenital Aganglionic Megacolon

Postoperative Complications	Total Number With Complications	Nonfatal	Fatal
1. Recurrence of symptoms; inadequate colon resection.....	4	3*	1
2. Infarction of proximal segment; anastomotic separation.....	3	0	3
3. Anastomotic stricture	1	0	1†
4. Inadequate blood replacement.....	1	0	1‡
5. Intestinal obstruction due to postoperative adhesive bands....	1	1	0
Total.....	10	4	6

* All successfully treated by secondary colon resection.

† Fatality due to cardiac arrest during secondary procedure.

‡ Parents religious convictions prevented adequate blood replacement.

incomplete resections were relieved of symptoms by the resection of an additional segment of the colon or rectum.

A series of "step frozen sections" are taken at intervals of 5 to 6 cm., beginning in the dilated rectosigmoid colon. An average of six such sections were required. Two techniques for excision of tissue for "frozen section" study were employed. In one of them, a small segment of the full thickness of the colonic wall was removed, while in the other a segment of the muscular layers was excised without opening the mucosa.

An attempt was made to sterilize the colon in preparation for operating by giving antibiotics or chemotherapeutic agents by mouth. Succinyl sulfathiazole was used in early cases, later the tetracycline drugs, and in the more recent procedures neomycin, 250 mg. every six hours for three days.

Preliminary Colostomy

Ten patients with congenital aganglionic megacolon required colostomy decompression (appendicostomy in one case) because of failure of enema to relieve obstruction. The oldest infant in this group was four months of age. In all other infants and children decompression and preparation for operation was carried out without need for colostomy.

Four of the patients died following colostomy, the oldest at four months of age. Two children are awaiting definitive operation with well functioning colostomies. Attempt was made to perform pull-through procedures following colostomy in three patients less than six months of age, and two of them died (see Table 3).

Postoperative Deaths and Complications

There were six postoperative fatalities and four additional major, nonfatal complications following these 23 operative procedures. In three cases death followed local infarction of the proximal segment of colon or was associated with apparent anastomotic disruption. The unique aspect of this group was the extraordinarily low age at which the pull-through procedure was attempted (three weeks, three months,

and five months of age). There seemed to be no other common factor. Three additional complications in three children included: (a) Stricture at the site of anastomosis, (b) inadequate blood replacement, and (c) intestinal obstruction secondary to postoperative adhesive bands. The first two complications mentioned were fatal.

Obstructive symptoms recurred in four children, usually beginning within a month after the initial pull-through procedure. One died as a result of the complications of intestinal obstruction before a second resection could be performed. The three others were successfully treated by additional resection of colon or rectum. Four patients with mild anastomotic stricture responded to digital dilation and required no further operation.

ACUTE INTESTINAL OBSTRUCTION IN EARLY INFANCY

Among 31 patients with congenital aganglionic megacolon (operative and nonoperative) seen in this hospital since 1943, 26 required hospitalization for intestinal decompression during the first six months of life. The initial operative procedure or medical management was carried out in other institutions in most instances. In all of these patients, however, the eventual demonstration of an aganglionic segment was possible at operation or by repeated roentgenographic studies with barium enema. Eight of the infants had undergone exploratory laparotomy during the first 14 days of life. The preoperative history in these cases was unusual. The passage of meconium was first noted on the third or fourth day of life. The obstruction was intermittent, often temporarily relieved by enemata. The predominant preoperative diagnoses were volvulus of the midgut, malrotation of the colon or intestinal stenosis.

Operative Findings

Diagnostic observations at laparotomy were meager. In one case the postoperative diagnosis was "volvulus of the sigmoid or descending colon," apparently spontaneously reduced. In three instances no abnormality at all was seen.

TABLE 3.—Results of Therapy in Children with Congenital Aganglionic Megacolon Who Required Hospitalization in Early Infancy for Intestinal Obstruction*

Type of Therapy Employed	Total	Death: Postoperative or in First Year of Life	Lost to Follow-up	Alive at 1 Year	Alive at 2 Years	Pull-Through Operation After 2 Years of Age
Medical regimen (no operation or exploratory laparotomy (7) only	15	3	3	9	8	4
Colostomy or ileostomy.....	7	3	1	3	2	1
"Pull-through" operation during first 6 months of life.....	4	3	0	1†	0	0
Total.....	26	9	4	13	10‡	5

* Emergency hospital admission during the first 6 months of life.

† Died following secondary resection at 16 months of age.

‡ Five patients survived to 2 years of age prior to 1949. One of these was asymptomatic thereafter; 3 had severe symptoms during childhood; and one died from the complications of congenital megacolon at 8 years of age.

In two cases the possibility of aganglionic megacolon was discussed or suggested. The correct diagnosis was made at the time of exploration in only two of the eight infants. In the later four cases, mild dilation of the sigmoid colon was described.

The ultimate result of therapy in these eight cases was as follows: (a) Two patients died following a pull-through procedure performed under the age of four months; (b) two died of complications of megacolon, without operation, one at two months and one at 18 months of age; (c) one was lost to follow-up at six months of age; (d) two were successfully treated by a pull-through procedure after the age of two years; (e) one was successfully managed by a medical regimen for over four years. The mortality in this group was thus at least 50 per cent.

DISCUSSION

An operative approach to the problem of congenital aganglionic megacolon utilizing the pull-through principle was adopted in this hospital in 1949 and has been employed in 23 procedures during the subsequent five years. Although the basic operation has not been altered, several modifications and refinements now seem indicated.

The use of the "frozen section" technique in examination of the intestinal wall for ganglion cells in the myenteric plexuses is of great importance in establishing the site for proximal transection of the colon. When unequivocal ganglion cells are recognized by the pathologist in the proximal extremity of the resected segment, the anastomosis may be carried out without fear of recurrent obstruction. Similar studies of the distal margin are of academic interest only. Resection should be carried distally to the lower rectum in all cases without regard to the presence or absence of myenteric ganglion cells.

Both transperitoneal (Swenson) and extraperitoneal (Hiatt) resection of the dilated colon segment gave satisfactory results, and each has apparent virtues. The "step" technique for frozen section examination of the proximal colon can be adapted to either operative procedure. Biopsy specimens of the colon excised without entering the lumen are satisfactory for the recognition of ganglion cells.

In the small series presented, pull-through procedures were hazardous in the first year of life, and in general it is probably advisable to defer such operations beyond infancy. This is in striking contrast with the authors' experience with abdominoperineal procedures for imperforate anus, which are routinely carried out in the neonatal period with a relatively low mortality.

The recognition of congenital aganglionic megacolon in the newborn may be difficult, even at laparotomy. When the condition is known, the patient should be maintained on a medical regimen (enemata). Colostomy should be performed only when obstructive episodes threaten life.

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Rheumatic Fever in Southern California

Problems Related to Diagnosis

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IN ORDER TO DISCUSS the problem of rheumatic fever particularly as it occurs in Southern California, it is necessary first of all to define what is meant by the term *rheumatic fever*. It is the author's opinion that it must be thought of in its broadest meaning. Most diseases vary widely in the spectrum of their manifestations from the outspoken or unquestioned case to the more mild and difficult case to recognize clinically.

In a susceptible person a wide range of events can take place following streptococcal disease (Chart 1). Streptococci can be present in the nasopharynx of such a person without actually producing disease; in such an instance there is no immunologic evidence of invasion into the tissues by the organism. In another situation, in the same person, the streptococci may actually invade the tissues, producing the usual symptoms of streptococcosis² but not rheumatic fever. In a significant proportion of such susceptible persons, however, a streptococcal infection is followed after a short period by an *unusual* response of *certain tissues*, particularly in the heart, joints and skin. This unusual response will be considered herein to be *rheumatic fever*, whether it be mild or severe.

With rheumatic fever thus defined, certain questions can be posed and an answer will be attempted.

1. Does rheumatic fever occur in natives of Southern California?
2. Is there a difference in the incidence of streptococcal disease in Southern California as compared with other areas in the United States?
3. What is uncomplicated streptococcosis?
4. What are we going to accept as evidence of rheumatic fever?

Existence of Rheumatic Fever in Natives of Southern California

The author has made no inquiry into the actual number of individuals involved; but it is undeniable that rheumatic fever does occur in natives of South-

- Rheumatic fever occurs in natives of Southern California and is a cause of death.

The incidence of streptococcosis in Los Angeles is approximately equal to that in three other major cities in the United States where rheumatic fever is known to occur commonly.

Manifestations of rheumatic fever may range from mild to severe. It is suggested that a greater percentage of patients in Southern California have symptoms of rheumatic fever that are more mild.

Differentiation between prolonged, uncomplicated streptococcosis and rheumatic fever is a major problem. The judicious use of a battery of tests, acute phase reactants, on the same blood sample will frequently help to establish the diagnosis in borderline situations so common to Southern California.

ern California and is a cause of death. Rothman³ reported on a survey he conducted during the five-year period 1939-1943 which was limited to the number of deaths due to rheumatic fever in persons under 19 years of age. The data was obtained from Los Angeles hospitals and was rechecked at the Los Angeles Vital Statistics Bureau. Cases in which rheumatic fever developed prior to residence in California were not included. A total of 25 deaths occurred within the five-year period: Six in 1939, four in 1940, two in 1941, five in 1942 and eight in 1943. Autopsy was done in 17 of the 25 cases. In all the autopsy material one or more of the following were observed: Aschoff bodies; typical rheumatic valvular vegetations; mitral stenosis; pancarditis with no bacteriologic evidence of pyogenic organisms or tuberculosis.

Incidence of Streptococcosis Throughout the United States

A number of studies, including those from the armed services,¹ have shown a close relationship between the general overall incidence of streptococcal disease and the incidence of rheumatic fever. During epidemics of streptococcal disease the incidence of rheumatic fever has shown a proportionate rise, always being about 3 to 4 per cent of those infected with streptococci. In relation to the incidence of rheumatic fever in Southern California, a pertinent question would therefore be, "Is there a difference

This Study was supported by funds from the Los Angeles County Heart Association.

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Presented before the Southwestern Pediatric Society, May 20, 1955. Submitted July 15, 1955.

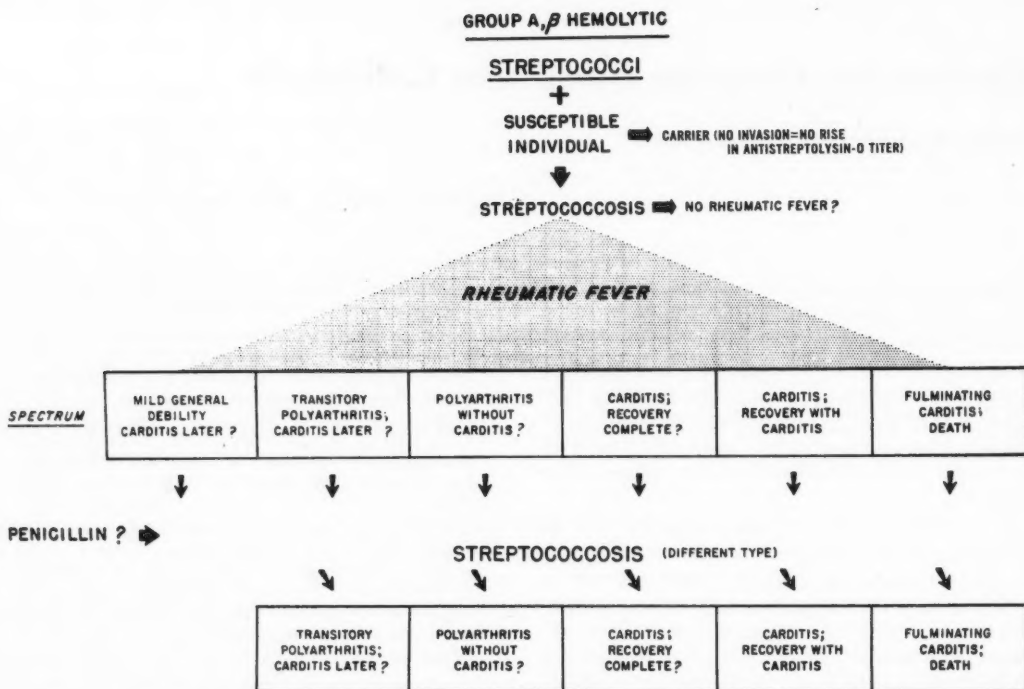


Chart 1.—Diagram illustrating the possible sequence of events when Group A β hemolytic streptococci come into contact with a patient who is susceptible to rheumatic fever. In instances in which rheumatic fever is a sequel, note the wide *spectrum* of possible manifestations of the disease.

in the incidence of streptococcal disease as compared with other parts of the United States?" Data obtained from Health Department reports would indicate that there is no pronounced difference in the incidence of streptococcosis between New York, Chicago, Salt Lake City and Los Angeles, when morbidity rates are considered. This is in spite of the fact that the first three mentioned cities are considered to have a high incidence of rheumatic fever. Chart 2 shows comparative rates for the cities Los Angeles and New York for the years 1930 to 1954.

What Is Uncomplicated Streptococcosis?

It would appear that whatever one is willing to accept as evidence of uncomplicated streptococcosis must automatically help to define what can be accepted as evidence of rheumatic fever. Can such a separation be made? Certainly the extreme ends of the spectrum reveal obvious differences, but can one draw a line in the center of the spectrum that separates streptococcosis from rheumatic fever?

Perhaps the problem could be resolved by definition based on a statistical concept. This way, knowing the response of the average person to the streptococci and knowing the variations of the response out to three standard deviations from the mean, one

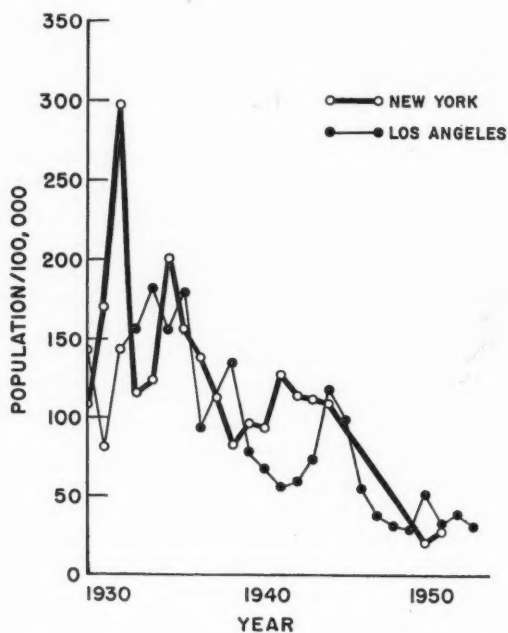


Chart 2.—Incidence of streptococcosis per 100,000 population in New York and Los Angeles.

TABLE 1.—Serologic Data—Normal Values for Acute Phase Reactants

Determination	Number of Individuals	Mean	Minimum	Maximum	Measurement
Mucoprotein-tyrosine	76	3.3	1.8	4.3	Mg. per 100 cc.
Antistreptolysin-0 titer	67	55	0	333	Todd units
C-reactive protein	76	0	0	2+	Mm. of precipitation
Nonglucosamine polysaccharides..	75	116	85	148	Mg. per 100 cc.
Sedimentation rate	7	3	11	Mm. in 1 hour (Westergren)

TABLE 2.—Serologic Data—Acute Phase Reactants in Various Disease States

Condition	Sedimentation Rate	Mucoprotein-Tyrosine	Antistreptolysin Titer	C-Reactive Protein	Nonglucosamine Polysaccharides
Acute respiratory disease	Normal or slightly increased	Normal or slightly increased	Normal	±	Normal or slightly increased
Streptococcosis	Normal or slightly increased	Normal or slightly increased	Increased	±	Normal or slightly increased
Acute rheumatic fever	Increased	Increased	Increased	+	Increased
Acute glomerulonephritis	Increased	Increased	Increased	+	Increased
Acute rheumatoid arthritis	Increased	Increased	Normal	+	Increased
Smoldering rheumatoid arthritis	Normal	Increased	Normal	±	Increased
Inactive rheumatic fever	Normal	Normal	Normal	0	Normal
Malignancy	Increased	Increased	Normal	+	Increased
Lupus erythematosus	Normal or increased	Increased	Normal	±	Increased

could then call *abnormal* any response which was greater than three standard deviations from the mean. In more specific terms, this response would be measured by such items as:

1. Prolonged symptoms of acute infection following streptococcosis—that is, fever, malaise, anorexia, tachycardia, evanescent pain.
2. Prolonged laboratory evidence of acute infection following streptococcosis—anemia, leukocytosis, conduction disturbances on the electrocardiogram, and elevation of the acute phase reactants.

By such a technique one could arbitrarily define uncomplicated streptococcosis and rheumatic fever. This would do little to help toward an understanding of the fundamental disturbance or disturbances in rheumatic fever, but perhaps it would permit clearer thinking regarding the problem as it relates to Southern California where the extreme end of the spectrum of severe rheumatic fever is less commonly seen.

Value of the Acute Phase Reactants

In borderline situations such as those referred to in the foregoing paragraphs the performance of a battery of the acute phase reactant tests on the patient's blood will frequently help to establish the correct diagnosis when taken into account with the

clinical findings. The performance of such a battery of tests is analogous to the situation in liver diseases where one seldom performs a single liver function test, but rather uses a battery of tests to establish the diagnosis. The acute phase reactants are: Sedimentation rate, antistreptolysin-0 titer, mucoprotein-tyrosine, C-reactive protein, nonglucosamine polysaccharides, hexosamine polysaccharides, hyaluronidase inhibitor, complement. Normal values for certain of these acute phase reactants as determined in the laboratory of the department of pediatrics at the University of California at Los Angeles School of Medicine are shown in Table 1.

For the past two to three years the laboratory has been making such determinations in a number of situations. The results are summarized in Table 2. In analyzing this table it is obvious that the main difference between acute respiratory disease of nonstreptococcal origin and streptococcosis is the increased antistreptolysin titer found in streptococcosis. In acute rheumatic fever, all of the acute phase reactants are elevated and usually greatly so. The same is true for acute glomerulonephritis. In acute rheumatoid arthritis all of the acute phase reactants are generally elevated except the antistreptolysin titer. Why this is so is not apparent at present, but certainly this can be helpful in differentiating these two rheumatic diseases that are so

greatly different as to prognosis. In smoldering or subacute rheumatoid arthritis generally only the mucoprotein is elevated. In malignant disease and lupus erythematosus the acute phase reactants are generally elevated except for the antistreptolysin titer.

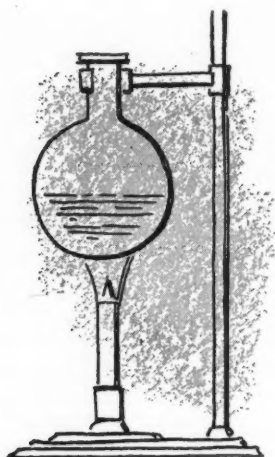
To repeat, the main value in such a battery of tests, performed on the same specimen of blood, would be to help differentiate these conditions, one from another, in borderline situations. Since this is so common a problem in Southern California, such

a battery of tests is highly desirable and can be readily performed by the average good laboratory.

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An Improved Intravenous Contrast Medium

Preliminary Studies with Hypaque®

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GEORGE JACOBSON, M.D., Los Angeles

DURING THE last two decades there have been many substances used for intravenous urography and constant work is being done to develop a contrast medium which is nontoxic and has a good radiographic density. The purpose of this presentation is to report on the use of a new iodine-containing compound, Hypaque®, in 50 consecutive examinations.

Hypaque (sodium 3,5-diacetamido-2,4,6-triiodobenzoate) is a white crystalline solid which contains 59.87 per cent iodine and is highly soluble in water. The iodine content of Hypaque is slightly less than that of Urokon® (sodium acetrizoate 3-acetylaminio-2,4,6-triiodobenzoic acid) which contains 65.8 per cent iodine. Diodrast® (3,5-diiodo-4-pyridone-N-acetic acid diethanolamine) contains 49.8 per cent iodine and Neo-iopax® (sodium iodomethamate, disodium salt of N-methyl-3,5-diiodochelidamic acid) contains 51.5 per cent iodine.

In anesthetized dogs, rapid injection of Hypaque in dosage up to 4,000 mg. per kilogram of body weight produced no change in the heart rate, blood pressure, respiration, or autonomic function.⁵ At a dosage of 8,000 mg. per kilogram, respiratory arrest and later cardiac arrest occurred. It was also found that there was slight inversion of the terminal portion of the T-wave at the 1,000, 2,000, 4,000 mg. per kilogram dose levels. The compound was excreted almost entirely through the kidneys. The rate of excretion was rapid since most of the administered drug was eliminated within two hours and over 90 per cent was excreted within 24 hours. Porporis³ has reported similar results in excretion studies using Urokon.

In tests with rats, cats and mice, it was observed that the acute toxicity of Hypaque was less than that of other contrast media.⁵ Rhesus monkeys receiving Hypaque intravenously had no casts in the collecting tubules whereas in monkeys receiving various other media, casts developed in the collecting tubules of the kidneys. With toxic doses, Hypaque and the other contrast media produced similar reversible pathological changes in the kidneys, liver and lungs.

All material used in this study was supplied by Winthrop-Stearns, Inc.

From the Departments of Radiology, School of Medicine, University of Southern California, and the Los Angeles County General Hospital. Submitted July 22, 1955.

• A relatively new intravenous opaque medium, Hypaque® in 50 per cent solution, was used in 50 consecutive patients. None of them had a serious reaction. Twenty-two had mild reactions which were of no clinical significance. The radiographs obtained seemed to be equal in quality to those obtained with other contrast media.

METHOD OF STUDY

The patients were prepared for excretory urography in the usual manner. Before injection, a history was obtained with regard to allergic sensitivity and previous reactions to other compounds containing iodine. Temperature, pulse rate, respiration rate and blood pressure were recorded before the radio-

TABLE 1.—Reactions in 50 Patients Following Intravenous Injection of 30 cc. of 50 Per Cent Hypaque®

Symptoms	No. Patients with Reaction	Severity	Duration
Nausea	4	Minimal	1 or 2 minutes
Vomiting	0		
Excessive sweating	1	Minimal	Seconds
Excessive salivation	2	Minimal	During entire examination
Choking sensation	0		
Wheezing	0		
Dyspnea	0		
Cyanosis	0		
Flushing of skin	2	Minimal	2 to 3 minutes
Extreme pallor	0		
Pruritus	0		
Facial edema	0		
Sneezing	0		
Urticaria	1	Localized to neck, minimal	3 minutes
Venospasm (Local infiltration?)	2	Mild	3 minutes to few seconds
Other reactions—	4	Mild	Few minutes
Bitter taste, peculiar taste			
Elevation of temperature 1½ minutes after injection	1	Minimal	
Fall in systolic blood pressure	4	Minimal	
Increase in pulse	1	Minimal	
Total.....	22		

graphic examination was begun. A sensitivity test, in which 2 cc. of Hypaque was injected intravenously, was done in each case. Following this, 30 cc. of 50 per cent Hypaque was injected in approximately 30 to 45 seconds. Fifteen and thirty minutes after injection, the pulse, temperature, respiration and blood pressure were again recorded. All reactions, even those of a minor nature, were tabulated (Table 1). Radiographs were taken at 5, 10, 25, and 45 minutes after injection of Hypaque.

REACTIONS

In 50 consecutive examinations, there were 22 patients who had minor reactions (Table 1). Immediately after injection, four patients experienced a slightly bitter or metallic taste. During the first 15 minutes after injection, four patients had a decrease in systolic blood pressure ranging from 10 to 20 mm. of mercury. However, the blood pressure was back to normal at the termination of the examination. Two patients had slight pain in the shoulder which could have been attributed to venospasm. The pain lasted a few seconds in one patient, and in the other it persisted for two or three minutes. One patient had mild urticaria. It was localized to the neck.

The remaining ten patients had minimal symptoms which included slight nausea or a slight feeling

of flushing. None of the patients had severe nausea and none vomited. All of the reactions recorded were minor and were considered insignificant.

The series was too small, of course, to permit acceptable conclusions, but the incidence of reactions compared very favorably with the incidence reported with Diodrast,² Neo-iopax⁴ and Urokon.¹

Although no specific measurements were made of the density of the excreted contrast medium, it was the impression of the authors that the radiographs were equal in quality to those obtained with other contrast media.

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Meningoencephalitis and Pneumonitis Due to Western Equine Virus

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WESTERN EQUINE ENCEPHALITIS is defined as a neurotropic virus disease of the nervous system.¹ It is an immunologically and pathologically distinct disease.^{1, 2, 8, 10, 11, 12} The term encephalomyelitis appears to be a misnomer which should be discarded in favor of meningoencephalitis, or just encephalitis;^{3, 5} meningeal involvement was noted in all cases in which autopsy was done in a series herein reported upon, and in all clinical cases there was at least equivocal evidence of meningeal irritation.

Any discussion of the encephalitides *in general* would be completely unrealistic, for the clinical features, sequelae, mortality and etiologic factors are widely variable as between patients and specific disease entities. What is known of encephalitis lethargica for example, does not necessarily apply to Western equine encephalitis; and although poliomyelitis is not often thought of as encephalitis, actually nonparalytic poliomyelitis is a true meningoencephalitis. In the present series of 20 cases only two patients gave a history of localized weakness and in only one was any objective evidence of localized weakness noted clinically. Since clinical evidence of meningitis was present in many cases in the series and myelitis was relatively rare, it is felt that the term Western equine encephalomyelitis should be dropped except in cases in which myelitis is indeed present.

ETIOLOGY

The Western equine encephalitis virus was isolated in horses in 1931 in the San Joaquin Valley by Meyer, Haring and Howitt.⁶ It was isolated in human cases in 1938.¹² The Western equine encephalitis virus is a medium-sized virus and all four of Koch's postulates have been fulfilled in establishing it as an etiologic agent in encephalitis. However, it is clinically indistinguishable from the other encephalitides except for the help given in diagnosis by the known geographical distribution of the encephalitides.

The recently reported California encephalitis virus⁹ is probably only one of several encephalitis viruses which have not yet been isolated. In this

• In a series of 20 cases here presented in a study of Western equine encephalitis, only ten were conclusively proven by serological or histopathological methods, while the other ten were presumptively cases of that disease. Involvement of the spinal cord was of relatively low incidence. In only one case of four in which autopsy was done could the Western equine virus be demonstrated in the cerebral tissues.

There was a rather high incidence of involvement of the respiratory tree. A high proportion of patients had complaints referable to the respiratory tract. Physical signs denoting disease of both the upper and lower respiratory tract, x-ray evidence showing bronchial and pulmonary involvement, and autopsy evidence of bronchopneumonia were noted frequently.

All patients had fever as well as symptoms and physical signs of central nervous system disease. Differential diagnosis posed many interesting and challenging problems.

The clinical features were those of meningoencephalitis and never a "flu-like" syndrome, although in several of the cases diagnosis could not be made with certainty for several days, until meningeal signs developed, and usually the patients were treated with one or several antibiotics during that time.

In all cases in which a neutralization test for the Western equine virus was done, the result was either positive or inconclusive. Results of complement fixation tests were significant in only six cases. In seven of 13 cases in which x-ray films of the chest were made, streaks of increased density were noted.

connection it may be noted that when the author first started summarizing cases from the Tulare County Hospital files during the height of the epidemic of 1952, there were about 30 cases that seemed likely to be later proven Western equine encephalitis. Yet each time the cases were reviewed, the number became smaller. Many of the patients had received antibiotics and it was impossible to be certain on admission whether the condition was a healing bacterial meningitis, nonparalytic poliomyelitis, or encephalitis. Some cases were never clinically distinguished from nonparalytic poliomyelitis. Many of the cases that were excluded from the series were probably encephalitis. A few of the cases that were included may be open to criticism. Finally the series was narrowed down to 20 cases,

Submitted February 4, 1955.

of which only ten were proven beyond shadow of doubt to be Western equine encephalitis.

Finley and Hollister⁵ stated that a proven case of Western equine encephalitis is one in which there is demonstrable antibody titer rise in the patient's blood or the virus is isolated from brain tissue. Hamilton⁸ also expressed the opinion that the diagnosis must rely on complement fixation or neutralization tests. In six cases in the present series, definitely positive titers were shown on serial complement fixations. In the others the complement fixation test results were either negative, inconclusive because of a low or nonrising titer, or were not done because the patient died too soon. In only two cases were the results of neutralization tests definitely positive. In seven other cases the neutralization test was reported as showing antibodies present but in inconclusive amount. In five cases, the neutralization test result was not reported, and in six cases not requested.

At autopsy the virus was isolated from brain tissue by inoculation on a chick embryo in only one case. Unfortunately in the other cases the bodies were embalmed before permission for autopsy could be obtained.

It is obvious that serologic methods are by no means entirely accurate. It is also probable that there are encephalitides for which there are no complement fixation or neutralization tests because the organism has never been isolated.

Lenette and Longshore¹² studied 1,097 cases of infectious encephalitis in California between 1945 and 1950 and noted that in 47 per cent of the cases no known virus could be demonstrated. They also noted that most of the cases of Western equine encephalitis were in Kern, Fresno, San Joaquin and Tulare counties. In most of the cases outside those counties, in patients who had not recently been there, the results of serologic tests were negative. Finley and Hollister⁵ reported a similar observation.

Adams and Weinstein¹ expressed the opinion that the correct diagnosis of encephalitis requires the aid of laboratory methods. Unfortunately, results of laboratory studies in this disease are often more confusing than helpful.

EPIDEMIOLOGY AND PATHOGENESIS

Epidemics in Manitoba, Saskatchewan³ and North Dakota⁷ have been described. Cases have been reported in Illinois.¹¹ In California practically all the proven cases of Western equine encephalitis are from the San Joaquin Valley; it is generally recognized that cases of encephalitis originating in Los Angeles and the San Francisco Bay area are rarely proven serologically to be due to the Western equine

encephalitis virus.⁹ Practically all of the literature pertaining directly to Western equine encephalitis virus is found in CALIFORNIA MEDICINE. Most reports in other journals refer usually to encephalitis in general and are given generalizations about the encephalitides which do not ordinarily apply to each of the specific types.

The Tulare County Public Health Department⁴ reported 32 proven cases of Western equine encephalitis with six deaths in the epidemic of 1952, which corresponds with the present series of 20 cases with four deaths.

Because of the relationship of the disease vector to standing water and mosquitoes, knowledge of geographic features of this area is necessary for an understanding of the problem of health department officers in attempting to control the epidemic. The Central Valley of California is a completely land-locked valley approximately six hundred miles long and varying from fifty to a hundred miles in width. The mountains protect the area from all the lower nimbus clouds so that the weather is exceptionally mild, especially in the San Joaquin, which is the southern half of the valley. Rainfall is scant. The entire Valley is now a network of irrigation ditches. The principal product of the area is cotton and irrigating it entails the flooding of huge areas of land. Any dip in a field can hold water for some time. In warm weather, the *Culex tarsalis* and *Aedes aegypti* mosquito can develop from the egg to the adult stage in about four days. These factors combine to make an almost insurmountable problem for the local health departments and mosquito control districts.

According to Lenette and Longshore,¹² even though cases of encephalitis are reported throughout the year, laboratory-confirmed cases of encephalitis are found only in July, August and September, and the serologically negative cases are probably due to a yet undiscovered virus. Of the 20 cases in the present series, all but two occurred between the beginning of June and the end of September. One was in April and one in October. Not until after the first of July was the first case in the series diagnosed—at autopsy; and the last diagnosis was made on a patient admitted to Tulare County Hospital on the second of September with a complement fixation of significant titer. The first case reported in our series did not have complement fixation and neutralization tests were not done in the first case in the series, for encephalitis was not being considered at that time. It is worth noting that there were many other cases of possible and probable encephalitis during the height of the epidemic, but not so diagnosed.

Table 1 shows the incidence in this series by sex, race and age. The ratio of male to female patients

TABLE 1.—Incidence of Western Equine Encephalitis by Sex, Race and Age in 20 Cases

Sex		Race		Age							
M	F	White	Mexican	Under 1 yr.	1 to 10	10 to 20	20 to 30	30 to 40	40 to 50	50 to 60	60 to 70
16	4	85%	15%	4	3	2	2	3	3	2	1

was 4:1. In other reported series¹² the ratio was 2:1. It has been suggested that the sex difference is owing to women's presumably lesser exposure to mosquito bites (since they are, in general, outdoors less); but in the area of this study, that may not be a very large factor, for a large proportion of the female population is employed in agricultural work in the open.

Three of the patients were of Mexican extraction, the remainder Caucasian. General hospital and clinic patients in the area are about evenly divided between the two races.

It is generally conceded that Western equine encephalitis is a disease of man and horse which occurs mainly in the Central Valley of California. It is less generally accepted that man and horse are only accidental hosts.⁵ The *Aedes aegypti* and *Culex tarsalis* mosquitoes are the vectors of this disease.^{2, 5, 6}

One of the main missing links in epidemiology is in the identification of the reservoir. Although some believe that the horse is the reservoir, the preponderance of evidence points to an avian reservoir. The domestic fowl has been proven to be a short-term reservoir, and the chicken mite has been suspected but not completely incriminated in epidemics, even though the virus has been found in the mites.¹⁰ The encephalitis virus is not passed from man to man, from horse to horse or from horse to man. In Kern County, California, and Yakima Valley, Washington, some wild birds have been proven to be hosts and their nests have been found to be infested with various species of arthropods that transmitted the Western equine virus.¹⁰ The life cycle of the virus is complex and not understood. It is felt that spinal fluid, blood, pharyngeal washings and feces are useless for isolating the virus under present methods, and only brain tissue from autopsy material has been found to yield the virus with any degree of regularity. However, the recently described technique of obtaining positive blood cultures for the poliomyelitis virus gives some encouragement.¹⁶

The virus has been isolated from mosquito pools frequently in early summer by the California State Department of Public Health's Encephalitis Study Unit.

It is generally accepted that the disease is transmitted from bird to man, or from bird to horse, by the mosquito vector. When the mosquito bites the

accidental host, the virus finds its way to the central nervous system—whether through the blood stream or by migration along the peripheral nerves is not known. The exact incubation period in man is very uncertain. How the virus finds its way to the respiratory tract is also uncertain, but it would seem more plausible that the vascular system carries the disease to the respiratory tract, rather than that there is a migration along the nerves. Recent work demonstrating a true viremia in poliomyelitis lends weight to this concept.¹⁶ The isolation of the lymphocytic choriomeningitis virus from the blood of patients during the acute disease also bolsters the theory.¹⁷

CLINICAL AND PATHOLOGIC FEATURES

In almost all cases in the series meningeal involvement was noted either clinically or at autopsy. Two of the patients complained of cough and two had positive pulmonary findings; five had symptoms compatible with involvement of the upper respiratory tract. X-ray films of the chest were done in 13 cases and in seven of them there was very definite evidence of pulmonary involvement. Radiographically there seemed to be a predilection for the right lower lobe, although other parts of the lower respiratory tract were also involved.

Autopsy was done in four cases. In one, only the head was examined. Bronchopneumonia was present in two of the other three cases, as was myocarditis. In one case a chromophobe adenoma of the pituitary (doubtless unrelated to the viral disease) was observed. Examination of the spinal cord was done in only one case, and edema only of the lateral and anterior horns was noted. The ganglia themselves appeared normal microscopically.

Examination of the autopsy summaries in these cases might lead one to conclude that the bronchial pneumonia noted in two cases was of a terminal nature. However, in light of the rather high incidence of respiratory signs and symptoms plus positive radiological evidence of pulmonary involvement in other cases in the series, it would seem more logical to assume that the pulmonary involvement noted at autopsy was due to a primary inflammatory response to the Western equine virus (Figure 1). It is noteworthy that the lymphocytic choriomeningitis virus was found in consolidated lung tissue in one fatal case of lymphocytic choriomeningitis.¹⁷

The autopsy summary of one case, in which the

lungs were normal, described an acute myocarditis with minute epicardial petechiae. The latter can be a manifestation of terminal hypoxia or of a possible terminal sepsis.¹⁵ In view of the known generalized nature of the disease, one might wonder—only in conjecture, of course—if the conditions noted could have been due to an acute viremia resulting from the Western equine virus.

As the author was not aware of the myocardial complications of some of the other encephalitides¹⁷ at the time the patients were being treated, routine electrocardiograms for evidence of myocarditis were not done.

SYMPTOMATOLOGY

The symptoms of Western equine encephalitis are primarily those of an inflammatory disease of the central nervous system. Since the lesions may be scattered throughout the nervous system¹ the symptoms can be quite varied. Finley and Hollister⁵ reported a uniform distribution of the disease in ages six months to 60 years, which corresponds with our data in the present series. They also noted that in adults there are more males affected than females, and in children the sexes were equal. Fever, headache, lethargy, drowsiness and stiff neck were the most common symptoms during the first three days of the illness. One-third of adults were reported to have tremor, while in children convulsions were quite common. These data also coincide with observations in the present series.

Kohut¹¹ reported a case in which the primary complaint was looseness of stools. Upon physical examination, drowsiness, plucking movements of the fingers, rigidity of the extremities, pharyngitis and diffuse abdominal tenderness were noted. Kohut said that a "flu-like" syndrome is present in all encephalitis. Although symptoms of involvement of the respiratory tract were present in a high proportion of the cases in the present series the symptomatology was more that of a central nervous system disease than of respiratory. Although rigidity and choreiform movements are reported to be common in other types of encephalitis, with the exception of nuchal rigidity, these conditions were rarely observed with Western equine encephalitis in the present series. A fairly sudden onset is common in children;² usually it is more insidious in adults.

History-taking was extremely difficult in this series, for many of the patients were brought in and left by the local police, by a helpful neighbor or by an employer and were unable to give a history. Many of the patients were migratory agricultural laborers, and many had no immediate family available. Follow-up observation also was almost impossible for the same reasons.

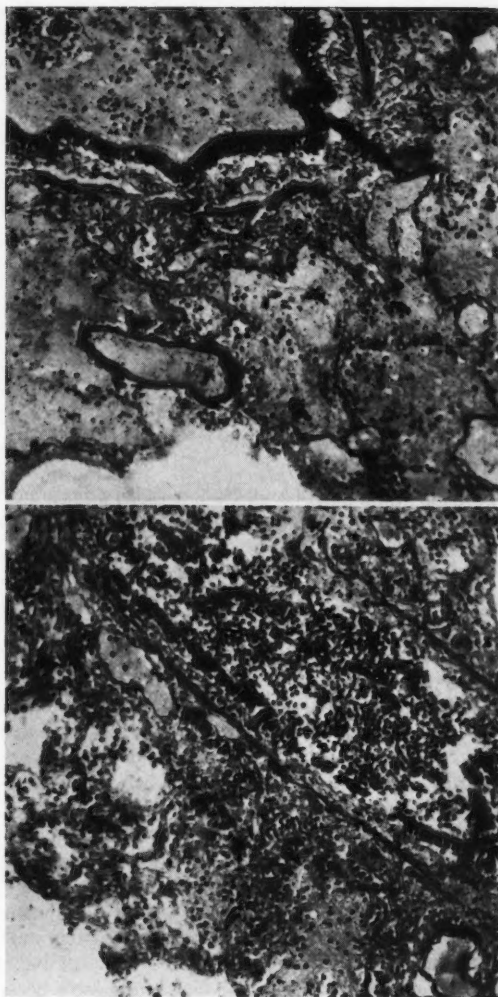


Figure 1.—Sections of lungs in which were noted bronchi filled with polymorphonuclear leukocytes and many alveoli filled with red blood cells and polymorphonuclear leukocytes. (X450).

The severe sequelae that are seen commonly in the other encephalitides are more the exception than the rule in Western equine encephalitis. There were none in the few cases in the present series in which follow-up was done.

Fulton and Burton,⁷ reporting on observation of 550 cases in Saskatchewan in 1941, noted that the symptoms were often confused with a "flu-like" syndrome, but that sequelae, which would occur some time after the acute infection, were proven by neutralization tests to be due to Western equine virus.

In the present series the main complaints (Table 2) were referable to the central nervous system

and all patients had complaints that were directly referable to the brain. This is very striking inasmuch as the numerical term 100 per cent has such a small applicability to medical statistics—even in small series.

Fever was the most common complaint. Although a history of fever was elicited in only 60 per cent of the cases, all patients were found to have fever upon examination.

Headache was a very common symptom but varied quite a bit in character in cases in which a description of it could be elicited.

It is interesting that at least equivocal nuchal rigidity was noted in 85 per cent of the cases on physical examination. The complaints of cough and earache are of interest when correlated with the physical findings referable to the respiratory tract.

As 35 per cent of the patients had previously received antibiotics to which they had not responded, an extremely difficult problem in diagnosis was raised, for the clinical and spinal fluid determinations in these cases would fit the clinical picture of either a viral disease of the central nervous system or a healing purulent meningitis. To withhold antibiotics in a purulent meningitis would be unnecessarily risking the patient's life. On the other hand, continuing antibiotics in a case of Western equine encephalitis would not only have no effect on the disease but would further cloud the diagnosis by foreclosing the opportunity of carrying out a therapeutic trial. In looking back over the cases which were excluded from the present series because of treatment with antibiotics, it is felt that some lives were probably saved by continuing antibiotic therapy.

SIGNS

Physical signs (Table 3) were a much more reliable index of diagnosis in the present series than were case histories. In all cases there was elevation of temperature ranging from 99.8°F. to 106.0°F. on admission. In all cases there were physical signs of central nervous system disease. Seventeen patients had nuchal rigidity. In the three cases in which nuchal rigidity was not present the patients died. Of the four comatose patients, three were in coma on admittance and the other became comatose afterward. All died.

It is felt that the rather high incidence (35 per cent) of positive physical findings referable to the respiratory tract may be significant, especially in view of the high incidence of respiratory tract involvement in lymphocytic choriomeningitis (20 per cent), mumps meningitis (13 per cent), and leptospiral meningitis (33 per cent).¹⁷

TABLE 2.—Incidence of Various Complaints and Symptoms in 20 Cases of Western Equine Encephalitis

Complaint or Symptom	No. Cases	Per Cent
Lethargy	4	20
Coma	3	15
Confusion	7	35
Delirium		
Disorientation		
Dizziness	2	10
Irritability	2	10
Convulsions	5	25
Fever	12	60
Headache	9	45
Malaise	6	30
No response to previous antibiotics	7	35
Stiff neck	7	35
Vomiting	5	25
Coughing	3	15
Head trauma	2	10
Localized weakness	2	10
Earache	3	15

TABLE 3.—Incidence of Various Signs of Western Equine Encephalitis in 20 Cases

Highest temperature	106.0° F.	
Lowest temperature	99.8	
Average	102.8	
	No. Cases	Per Cent
Nuchal rigidity	17	85
Disorientation	5	25
Coma	4	20
Lethargy	2	10
Twitching	4	20
Choreiform movements }		
Shakiness		
Babinski's sign	3	15
Absence of deep tendon reflexes...	4	20
Hyperactive deep tendon reflexes..	1	5
Localized weakness	1	5
Rigidity	1	5
Hamstring spasm	2	10
Pupils irregular	1	5
Bulging fontanelle	2*	10
Pulmonary findings	2	10
Pharyngitis, tonsillitis or otitis media	5	25

* Three of the patients in the series were infants.

That so few patients had reflex changes indicating spinal cord involvement indicates that this disease is not primarily myelitic.

After reviewing the data on suspected cases a number of times, the author has come to the conclusion that a positive diagnosis of Western equine encephalitis is almost impossible upon initial examination even at the height of an epidemic. It can also be concluded that a negative result of a complement fixation or neutralization test does not rule out encephalitis and diagnosis can best be made by reviewing the patient's chart months after he has left the hospital. In many typical cases results of complement fixation tests were negative and neutralization tests inconclusive. In many cases thought to be nonparalytic poliomyelitis, results of complement

fixation and neutralization tests were positive. A number of patients who were thought on admission to have typical cases of Western equine encephalitis, were later proved at autopsy to have granulomatous meningitis. Therefore, if the cases of granulomatous meningitis and the cases in which the patient had already received antibiotics be disregarded, it would seem that a diagnosis of encephalitis would be easy except for the fact that complement fixation and neutralization tests do not always distinguish what type of encephalitis is present.

LABORATORY, RADIOGRAPHIC AND CLINICAL OBSERVATIONS

Data on laboratory, roentgenographic and clinical observations were as follows:

Blood: The number of leukocytes varied from 6,250 to 16,500 per cu. mm.—in most instances in the range of 12,000. The proportion of segmented neutrophils varied from 31 per cent to 83 per cent, with a mean of 61 per cent; the proportion of stabs from 0 to 35 per cent with a mean of 10 per cent, and of monocytes from 0 to 13 per cent with a mean of 3 per cent.

Urine: Urinalysis was recorded in all but two of the 20 cases. In seven, definite abnormalities were noted. One patient had 4+ albumin with gross blood, one had 4+ albumin with a few leukocytes, two had positive reaction for albumin and both erythrocytes and leukocytes, two had leukocytes only and one had albumin only. It is noteworthy that not all patients with hyperpyrexia had abnormalities in the urine, nor was there any correlation of urinary abnormality with any of the other data in each case or with clinical progress. Three of the patients with urinary abnormalities were over the age of 50, and in them the condition may not be relatable to the disease; but three were under 30 years of age.

Spinal Fluid: Spinal fluid pressure was not determined in all cases, partly because of the difficulty in holding the disoriented patients still during the spinal tap and partly because there were not enough manometers available owing to the greatly increased need in an epidemic situation.

The spinal fluid cell content varied from 67 to 600 per cu. mm., with the exception of one case in which there were 9 cells per cu. mm. The mean cell count for all cases was 243. The proportion of polymorphonuclear cells varied from 5 per cent to 89 per cent, with a mean of 36 per cent. Early in the epidemic the polymorphonuclear cells predominated, but late in the epidemic the mononuclear cells predominated at the time of admittance to hospital. There appeared to be no correlation be-

tween the number of cells in the spinal fluid and the differential proportions; nor was there any correlation between these factors and the results of the complement fixation and neutralization tests for the Western equine virus.

The spinal fluid protein content in most cases was at the top of the normal range, although the variation was great, ranging from 15 mg. to 102 mg. per 100 cc. The spinal fluid sugar content, however, was slightly high in most cases, but the determinations were not done concurrently with blood sugar determinations.

There was growth of organisms on spinal fluid cultures in three cases, but a different organism in each case and not the Western equine virus in any of them. It was assumed that these were contaminants.

Serological tests for Western equine encephalitis: Seven patients, including the first four and the last in the series, had no serological tests for the Western equine virus. Three of the seven were patients who died. In seven cases antibody was absent or present in insignificant amount as shown by the complement fixation test, while in six cases there was a significant rise in titer on serial tests ten days apart. In four of the latter, however, results of neutralization tests, were inconclusive, and in only two cases was the result positive. All of the cases in which the result was negative or insignificant for complement fixing antibody also had neutralization tests that were interpreted by the California State Department of Public Health Laboratory as being inconclusive either due to small amounts of neutralizing factor or failure to show a significant rise on serial tests ten days apart. None of the neutralization tests were negative for Western equine infection.

It is obvious from the clinical features in the present series that encephalitis cannot be ruled out on the basis of negative or inconclusive results of blood tests. If the complement fixation and neutralization tests for the Western equine virus are as accurate as they purport to be, then it must be concluded that some of the cases in the present series were due to some as yet unknown virus or viruses which have not been isolated and for which no serological test has been developed. Negative results of complement fixation and neutralization tests, then, may rule out Western equine encephalitis, but do not rule out encephalitis due to other viruses. In all cases results of serological tests were negative for St. Louis and mumps encephalitis.

Radiological Findings: In a review of the literature no mention could be found of pulmonary involvement by the Western equine encephalitis virus, even though many of the encephalitides start out as a "flu-like" syndrome. In seven of the 13

cases in the present series in which x-ray films of the chest were made, positive radiological evidence of involvement of the lower respiratory tract was noted. No abnormality was observed in the other six. The physical findings and autopsy findings are consistent with the x-ray findings of streaks of increased density extending outward from the hilum and usually in the right lower lobe. It has been noted that abnormalities in the lungs have been observed roentgenographically in Japanese encephalitis,¹⁴ mumps meningitis, and leptospiral meningitis.¹⁷ Streaks of increased density in the upper left lung field were seen in x-ray films of one of the patients. In that case complement fixation was positive for the Western equine virus in the dilution of 1:128 and the result of a neutralization test was inconclusive.

Course of the Disease: Each patient was ill from one to five days—average about three days—before being hospitalized. The temperature became normal usually on the third hospital day, but as early as the first day and as late as the ninth. Cerebration, however, did not return to normal quite so early and the period of hospitalization necessary for the spinal fluid and cerebration to return to normal varied from five to 21 days, with a mean and median of 14 days. During this time the patient seemed to be oblivious to his surroundings. Often the patient would complain of stiff neck or even of being “sore all over” for seven to ten days after admission. Patients with the latter complaint were included in this series only if results of complement fixation or neutralization tests were positive or if a thorough examination of muscles had been done by a physical therapist and no evidence of localized weakness found.

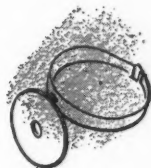
Three of the four patients who died were comatose when admitted and the other became comatose

one day after admission. Two died the day of admission, one on the second hospital day, and one on the seventh day.

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Leukoplakia of the Anus

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LEUKOPLAKIA is a precancerous dermatosis of mucous membranes analogous to senile keratosis of exposed skin surfaces. Leukoplakic lesions are seen most commonly in the oral cavity—in men more often than women at that site. They occur somewhat less frequently on the vulva. The bladder, kidney pelvis, ureters, larynx, esophagus, cervix and glans penis are occasionally involved. Extensions of primary vulvar leukoplakic lesions with involvement of the perineum and perianal skin have been described in the literature.^{1,2} Primary leukoplakia on the anoderm of the anal canal is rarely reported.^{4,15} The possibility of malignant transformation in untreated leukoplakia is well recognized. One-third of oral cancerous lesions originate in leukoplakia,^{11,12} and about one-fourth of the cases of vulvar cancer are associated with leukoplakia.^{8,14,18} The importance of early recognition and appropriate treatment of anal leukoplakia is therefore being emphasized.

Certain confusions exist in the literature concerning leukoplakia, kraurosis and other dermatoses in the vulvar and perianal region.¹⁷ This is possibly owing to conflicting concepts as to etiology and pathology and to variations in terminology between dermatologists, gynecologists, pathologists and others who may deal with conditions in this location. This lack of clarity has led to improper treatment and disabling operations for some of the relatively benign dermatoses that occur in this region.¹⁷

Leukoplakia is basically a chronic inflammatory hypertrophy in which anaplasia and malignant dyskeratosis may develop and subsequently advance to an invasive squamous cell cancer.^{8,11,18} Kraurosis is a progressive sclerosing atrophy found mainly on the vulva of aged persons. It is now considered to be a separate entity and of a relatively benign nature.^{3,13,17} However, leukoplakia can be engrafted upon kraurosis.^{14,16}

Anal leukoplakia is more likely to occur in the older age groups of either sex. Chronic irritation or trauma is probably a basic etiologic factor. Subjective symptoms are of no diagnostic significance. The clinical diagnosis of primary anal leukoplakia is indicated by single or multiple slightly raised,

• Anal leukoplakia is catalogued as precancerous because of the high incidence of malignant transformation found in lesions of this type.

Biopsy must be done to substantiate the clinical diagnosis of leukoplakia, to demonstrate the stage of the process, and to indicate the proper effective therapeutic approach.

Surgical excision is advisable in the early stage to avoid later carcinomatous changes and mutilating operations necessary for advanced malignant growth.

Three cases of leukoplakia involving the anoderm of the anal canal are presented herewith.

irregular, marginated, grayish-white keratinized patches in the anal canal. Tissue biopsy is necessary for confirmation. Initially, the process is slowly progressive hypertrophy of the epidermis with chronic inflammation in the subjacent dermis. The next clinical stage is evidenced by verrucous or ulcerative changes signifying probable malignant degeneration with anaplastic alterations in the epithelium in situ. If untreated, penetrating malignant growth may develop. Differential diagnoses to be considered include kraurosis extending perianally from primary vulvar involvement. Other innocuous dermatoses which sometimes occur about the anal region and which may at some stage resemble true leukoplakia in appearance, are lichen sclerosus et atrophicus, scleroderma, lichen planus and neurodermatitis with lichenification.^{7,9,17}

Treatment of anal leukoplakia depends on the stage of the lesion and should be initiated only after microscopic verification. The early or precancerous phase with small patches of leukoplakia will respond to local excision or electrosurgery. A more complete anoplastic procedure should be done for large patches, for verrucous and ulcerative changes, or when anaplastic changes are demonstrable microscopically.^{2,4} The presence of an invasive squamous cell cancer will necessitate radical resection of the rectum, as well as an inguinal node dissection. Radiation therapy has proved ineffective and impractical in the treatment of leukoplakia.

PATHOLOGY

Grossly, the appearance of milky or pearly-white, slightly elevated, irregular plaques in the anus is suggestive of leukoplakia. The term *leukokeratosis* has been reserved for thickened, verrucous patches.

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Later erosive surface changes often indicate epithelial anaplasia and possibly deeper invasion.

Microscopically, the basic changes resemble those of senile keratosis of the exposed skin and are variable in degree.^{10, 11, 13} The early or precancerous stage is essentially one of epithelial hypertrophy with variable hyperkeratosis and pronounced acanthosis in the epidermal layer, together with chronic inflammatory changes in the subjacent corium. Parakeratosis may be prominent. The Malpighian layer shows hyperplastic widening and prolongation of the interpapillary rete pegs. The dermis has a lymphocytic infiltrate and fibroblastic proliferation in the papillary and subpapillary layers. Malignancy starts as a squamous cell cancer *in situ* with some of the features of Bowen's disease.⁶ Atypism and malignant dyskeratosis in the prickly cell layer are the changes which advance the lesion from the precancerous dermatoses. Plasma cells are usually present in the dermis when anaplasia is found in the epidermal layer. The final stage is an invading cancer involving the dermis and deeper tissues.

Kraurosis, lichen sclerosus et atrophicus or scleroderma can occur perianally and may bear a superficial resemblance to leukoplakia because of varying hyperkeratotic surface changes.^{7, 9, 17} Histologically, in these lesions the prickly cell layer shows pronounced atrophy, and there is edema as well as homogenization of collagen in the upper corium. Lichen planus can sometimes be confusing, but in this condition there is edema in the dermis with a band-like lymphocytic infiltrate hugging the basal cell layer, and other corroborating skin lesions may be found elsewhere on the body.¹⁰ Neurodermatitis with secondary lichenification usually presents no problem in differential diagnosis.

In the three cases of anal leukoplakia presented herein, the lesions were in the precancerous phase and involved the anal canal proper.

REPORTS OF CASES

CASE 1. A 50-year-old white truck driver was first observed in April, 1950. During the preceding year, he had had increasing anal bleeding, prolapse and soiling. He said that he had treated himself for hemorrhoids a year before by inserting plumber's oakum—jute packing impregnated with creosote—into the anorectum. Severe pain, pronounced inflammatory reaction and progressive anorectal symptoms ensued.

Upon examination the anal orifice was observed to be atonic, with large hemorrhoids and mucosal prolapse. There was a transverse area of induration and thickening in the right posterior anal quadrant near the anorectal line. The anoderm at this site was pearly-gray, raised and extended into the adjacent rectal mucosa.

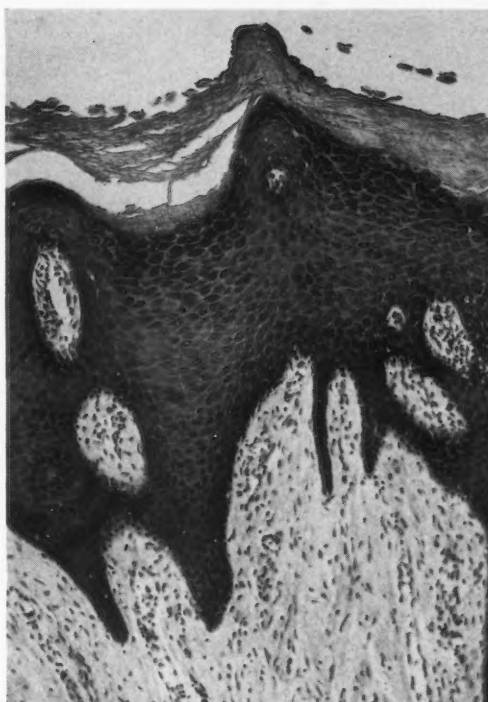


Figure 1.—Section of anoderm showing hyperkeratosis and prominent acanthosis with elongated rete pegs. There is an orderly hyperplasia of the Malpighian cells and a round cell infiltrate with scarring in the papillary layer of the dermis. ($\times 100$).

Hemorrhoidectomy, incorporating the keratinized areas, was carried out. Subsequent recurrences of thickened whitish plaques in the upper anal canal did not respond well to electrodesiccation. Wider excision of the recurrent leukoplakic areas was done in December, 1952, and after that the patient had no further difficulty. The pathologic diagnosis was anal leukoplakia (Figure 1).

Microscopically, there was pronounced cornification of the anoderm. Acanthosis was prominent, but the rete cells were orderly and the basal layer was well defined. Scarring and a mild degree of round cell infiltration were present in the papillary layer of the dermis.

CASE 2. A 63-year-old white lumberman was referred by a physician to the outpatient department of the University of California Hospital in June, 1952, because of severe anal leukoplakia. A biopsy report indicated "beginning malignant changes." According to the history, anal pain and nocturnal itching of increasing severity had been present for over four years. During the preceding two years, there had been bright red blood in the stools, which were the caliber of a pencil and passed with difficulty. In 1942 the patient had had a hemorrhoidectomy. Two years before he was examined in the

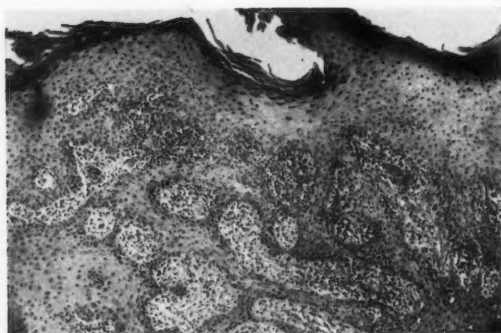


Figure 2.—Section of anal biopsy showing surface keratinization and pronounced acanthosis with deep anastomosing rete pegs. There is a profuse chronic inflammatory reaction in the papillary dermal layer. ($\times 65$).

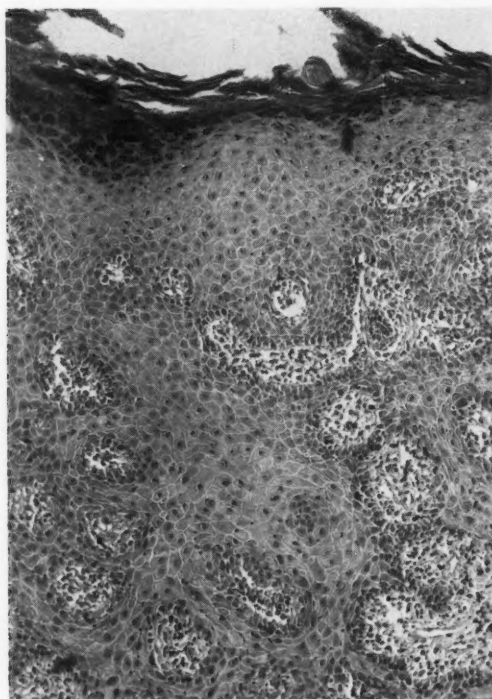


Figure 3.—Section of anal biopsy showing hyperkeratosis of the surface anoderm. The acanthotic prickle cell layer has an orderly hypertrophy and a uniform basal cell layer. No anaplasia is seen. The subjacent dermis shows a round cell infiltrate and plasma cells. ($\times 100$).

outpatient clinic he had had injection treatments for hemorrhoids, which aggravated the condition.

Upon examination the perianal skin was observed to be macerated, excoriated and thickened, suggestive of leukoplakia. Digital examination of the anus, which was stenotic and deformed, was very painful. The canal had marked leukoplakic changes and a

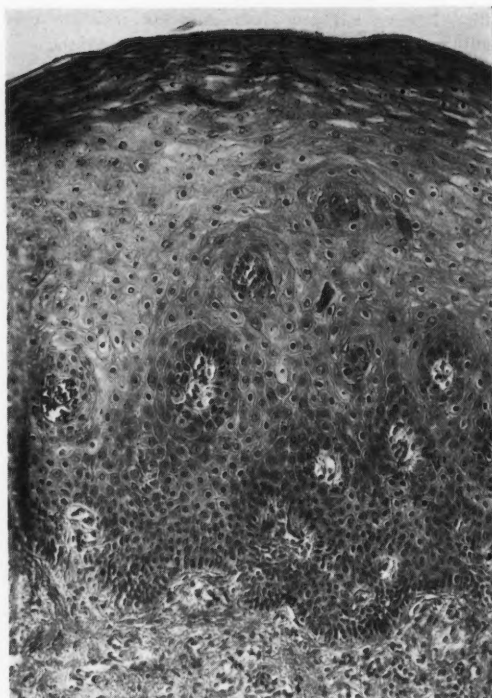


Figure 4.—Photomicrograph of anal biopsy showing parakeratosis in the corneal layer, an orderly hyperplasia of the Malpighian cells, a well defined basal layer and a round cell infiltration with fibrosis in the papillary layer of the corium. ($\times 150$).

chronic fissure posteriorly. Pathologic diagnosis after biopsy was leukoplakia of the anus (see Figures 2 and 3). Radiologists advised against roentgen therapy, and the patient was referred to the San Francisco Hospital for care. He returned home, however, and an abdominoperineal resection with colostomy was subsequently done elsewhere. The operative specimen showed anal leukoplakia but no anaplasia.

Microscopic study of the biopsy specimen taken at the time of examination in the University of California clinic showed thickened surface keratinization and pronounced acanthosis with deep anastomosing rete pegs. The hyperplastic prickle cells were orderly and the basal layer appeared intact. The dermis showed profuse chronic inflammation, with lymphocytes, plasma cells and large mononuclear cells in the papillary layer.

CASE 3. A 74-year-old white widow was referred to the outpatient department of the University of California Hospital in October, 1953, because of dysphagia due to esophageal diverticula. Upon routine medical examination it was noted that the anal canal was indurated, fibrotic and nodular, barely admitting the tip of the index finger. The patient had had a vaginal plastic operation and a clamp and cautery hemorrhoidectomy in 1941. Except for

the passage of small caliber stools, there were no complaints referable to the anorectum.

Examination showed a ring of large fibrous external tags and an everted anal canal with protruding fibrous polyps. Verrucous thickening and leukoplakic changes involved the stenotic upper anal canal and there was some extension to the rectum. Pathologic diagnosis of the biopsy specimen was leukoplakia of the anal mucosa (see Figure 4).

The patient refused to have surgical treatment because of her age; but continued observation during 1955 showed no clinical or pathologic advancement of the leukoplakic anal lesion.

Upon microscopic study of the biopsy specimen, surface keratinization and parakeratosis in the anoderm were noted. The acanthotic Malpighian layer had an orderly hypertrophy and an intact basal layer. The subjacent dermis had a round cell infiltrate and fibrosis.

DISCUSSION

In the three cases presented, the leukoplakia was in the precancerous phase and anaplastic or invasive changes had not yet occurred. The lesions developed on the so-called "mucosa" or anoderm of the anal canal, with some extension to the adjacent rectal mucosa. Extension to the perianal skin was noted in one case. Gorsch⁵ said that the lining of the anal canal is a transitional or modified type of squamous epithelium, lacking the cornification, hair follicles and sebaceous glands of the perianal skin. Epithelium of this type has poor resistance to irritative trauma.

The cause of leukoplakia is still a controversial subject.^{8, 15, 17} Syphilis was indicated by earlier investigators as a prominent factor in oral lesions. Deficiencies of vitamin A, hydrochloric acid, vitamin C and estrogens have been mentioned as causative factors in vulvar leukoplakia. Excessive excretion of irritating organic urinary acids has also been considered.¹⁴ The author believes that prolonged local irritation from any cause, acting on a deficient, aging epithelium, is fundamental. One of the patients reported upon herein gave a history of using a possible carcinogenic agent in self-treatment of hemorrhoids. Another patient mentioned difficulty following a clamp and cautery hemorrhoidectomy.

The patient who had a recurrence after local excision and electrodesiccation did well after a

second wider removal of the lesion. Verrucous, indurative or erosive changes suggest in situ or deeper malignant transformations and must be viewed with suspicion. A preliminary biopsy correctly interpreted will serve as a guide for a proper therapeutic approach. The patient in whom an abdominoperineal resection was performed (Case 2) would probably have done well with a less drastic anoplastic procedure. Study of representative biopsy sections in that case failed to show any anaplastic or invasive changes.

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Retroental Fibroplasia

A Reduction in Incidence Following a Decrease in Use of Oxygen Therapy for Premature Infants

ARTHUR H. PARMELEE, JR., M.D., IRVIN S. PILGER, M.D.,
and WALLACE O. AUSTIN, M.D., Los Angeles

THE EXACT INCIDENCE of retroental fibroplasia is unknown. It is known to vary in incidence from city to city, and between hospitals in a given city. Therefore, data on the incidence of this condition from year to year in individual hospitals is helpful in the evaluation of preventive measures. The only recent report of the incidence of retroental fibroplasia in a California hospital is one by Henry,⁵ who reviewed the incidence at the University of California Hospital in San Francisco for a three and a half year period up to the spring of 1954.

MATERIALS AND RESULTS

At the Harbor General Hospital, Los Angeles, approximately 2,000 babies are delivered annually and each year about 150 premature infants with a weight of less than 2,500 gm. at birth are cared for. These infants are cared for in a special premature unit containing seven "Isolette" incubators and four Armstrong old type incubators. In general, all babies under 1,800 gm. are placed in an "Isolette" incubator on admission. Since January 1952, one of the authors has examined the eyes of every premature infant in the nursery prior to discharge and has continued to observe in the outpatient department any in whom retroental fibroplasia developed.

In the three years from January 1952 to January 1955, there were 453 premature babies delivered at Harbor General Hospital and the overall mortality rate was 20.9 per cent. Retroental fibroplasia devel-

• The incidence of retroental fibroplasia in a general hospital for the period January 1952 to January 1955 was reviewed and it was noted that a sharp decrease in incidence was associated with a reduction in the intensity of oxygen therapy.

Retroental fibroplasia developed most frequently in the smallest premature infants and no cases occurred in infants weighing more than 2,000 gm. at birth.

oped in 14 (3.9 per cent) of the 358 surviving infants with birth weight of 2,500 gm. or less.

The incidence of retroental fibroplasia was further determined for each of various weight groups during this three-year period (Table 1). There were no cases in the group from 2,000 to 2,500 gm., an incidence of 6.6 per cent among survivors in the 1,500-2,000 gm. group, of 14.7 per cent in the 1,000-1,500 gm. group, and of 75 per cent in the less than 1,000 gm. group.

The data was further analyzed to determine the incidence for each birth weight group for each of the three years (Table 2). In the year 1952 there were seven cases of retroental fibroplasia, in 1953 five cases, in 1954 one case and none during the first half of 1955. The birth weight of the infant and the extent of the changes in the eyes in each case are shown in Table 3.

DISCUSSION

Soon after January 1952 when the program of examining all premature infants in the nursery for retroental fibroplasia was begun, several cases were

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Submitted September 17, 1955.

TABLE 1.—Data on Retroental Fibroplasia in Premature Infants, January 1952 to January 1954, at Harbor General Hospital

Birth Weight (in gm.)	Births	Survivors	Mortality Rate (Per Cent)	No. with RLF	Survivors with RLF (Per Cent)
Under 1,000	55	4	92.7	3	75.0
1,000 to 1,500	56	34	39.2	5	14.7
1,500 to 2,000	105	91	13.3	6	6.6
2,000 to 2,500	237	229	3.4	0	0
Totals	453	358	20.9	14	3.9

RLF=Retroental fibroplasia.

TABLE 2.—Incidence of Retrolental Fibroplasia in Relation to Birth Weight in Each of Three Years

Birth Weight	Births	Survivors	Mortality Rate (Per Cent)	No. with RLF	Survivors with RLF (Per Cent)
Under 1,000 gm.:					
1952	17	1	94.1	0	0
1953	18	2	88.8	2	100
1954	20	1	95.0	1	100
1,000 to 1,500 gm.:					
1952	19	13	31.6	3	23
1953	23	12	47.8	2	16.6
1954	14	9	35.7	0	0
1,500 to 2,000 gm.:					
1952	28	22	21.4	4	18.1
1953	39	32	18.0	2	6.2
1954	38	37	2.6	0	0
2,000 to 2,500 gm.:					
1952	86	84	2.3	0	0
1953	66	64	3.0	0	0
1954	85	81	4.7	0	0

RLF=Retrolental fibroplasia.

TABLE 3.—Weight at Birth and Extent of Ocular Changes in 14 Cases of Retrolental Fibroplasia

Cases	Race and Sex	Date of Birth	Birth Weight (in gm.)	Ultimate Eye Findings*	
1. Mexican	F	January 7, 1952	1,588	Cicatricial phase	Grade IV—Right eye Grade V—Left eye
2. White	M	February 22, 1952	1,673	Active phase	Stage I—Both eyes
3. White	M	March 10, 1952	1,503	Cicatricial phase	Grade V—Both eyes
4. White	F	March 23, 1952	1,353	Cicatricial phase	Grade V—Right eye Grade IV—Left eye
5. White	F	May 16, 1952	1,304	Cicatricial phase	Grade III—Right eye Grade IV—Left eye
6. White	M	October 13, 1952	1,531	Cicatricial phase	Normal —Right eye Grade III—Left eye
7. White	M	November 29, 1952	1,446	Cicatricial phase	Grade V—Both eyes
8. Mexican	M	January 6, 1953	1,644	Active phase	Stage II—Both eyes
9. White	F	January 28, 1953	1,000	Cicatricial phase	Normal —Right eye Grade IV—Left eye
10. White	F	February 22, 1953	964	Active phase	Stage I—Both eyes
11. White	M	April 3, 1953	1,389	Active phase	Stage I—Both eyes Normal —Both eyes
12. White	F	September 7, 1953	1,673	Active phase	Stage I—Both eyes
13. White	F	October 27, 1953	1,361	Cicatricial phase	Grade IV—Right eye Grade V—Left eye
14. White	F	February 22, 1954	964	Cicatricial phase	Grade V—Both eyes

* The classifications used are those recommended by the National Society for Prevention of Blindness (Am. J. Ophthalmology, 36:1333, Oct. 1953). The active phase is rated as Stages I through V, and the cicatricial phase as Grades I through V.

observed. This increased the concern of members of the staff with the cause and ways to prevent this condition.

In December, 1951, Szewczyk¹² in a preliminary report suggested misuse of oxygen and sudden episodes of anoxia or reduction of oxygen supply as the cause of retrolental fibroplasia. This was followed by a more extensive article in March, 1952.¹³ At the same time Ingalls⁷ presented evidence of the production of eye lesions in animals by subjecting the pregnant mothers to anoxia, and Ryan¹¹ in Australia related an increased incidence of retrolental fibroplasia in one hospital to the acquisition of incubators that maintained higher oxygen concentrations.

With this information implicating oxygen as an etiological factor either by overuse or misuse, a reevaluation of the care of premature infants at Harbor General Hospital was begun. "Isolette" incubators were being used for all infants under 2,000 gm. and it was general procedure to give oxygen routinely in amounts of six liters per minute and to continue this for several weeks, particularly for the smaller infants. During the year 1952, attempt was made to use somewhat less oxygen and to remove the infants from the high concentrations of oxygen slowly, as was suggested by Szewczyk.¹³ However, oxygen still was used in amounts of four liters per minute for several weeks. There was some difficulty in abandoning the concept of unrestricted

use of oxygen. There was no pronounced decrease in the incidence of retrolental fibroplasia during the remainder of that year or the next. However, gradually through 1953 and 1954 less and less oxygen was used and for shorter periods. Meanwhile, beginning in July, 1953, all babies under 1,800 gm. were given a special low electrolyte formula* as recommended by Hepner and Krause.⁶ Routine use of the formula was discontinued in September, 1954. During this interval retrolental fibroplasia developed in three infants receiving the formula.

By early 1954, in light of continuing reports seeming to indict excessive use of oxygen,^{1, 9, 10} the amount of oxygen used for premature infants had been reduced to about two liters per minute and it was given for shorter periods. In the late spring of 1954, the use of oxygen was decreased to minimal amounts, and then only for obvious indications of respiratory distress and never longer than a day or two at a time. In June, 1954, use of an oxygen analyzer to determine the oxygen content of the incubators was begun and oxygen concentration was maintained at less than 40 per cent, as was suggested by Lanman,⁸ Gordon⁴ and Ashton.² At the time of this report there had been no cases of retrolental fibroplasia in 16 months, the most recent case having developed in February, 1954.

Even the tiniest babies seem to do as well with the minimal amounts of oxygen as they did previously when high concentrations were used for long periods. This agrees with observations made by Engle and Levine³ in a thorough study of the same subject.

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*Supplied by Mead Johnson & Co. as Formula 411.

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CASE REPORTS

Erythema Multiforme Exudativum; Treatment with Corticotropin

WOODROW MILLER, M.D., Beverly Hills

TREATMENT of erythema multiforme exudativum has been unsatisfactory until recently. Sulfa drugs, penicillin and newer antibiotics did not have therapeutic effect. Several reports emphasized dramatic improvement in the course of the disease following institution of cortisone or corticotropin (ACTH).^{1, 3, 5, 9, 10} This effect upon the disease has been advanced to support a theory that hypersensitivity is a basic factor in the syndrome.

Erythema multiforme exudativum has been described in the literature under many names (Stevens-Johnson syndrome, eruptive fever, Hebra's erythema multiforme exudativum, Behcet's syndrome, ectodermosis erosiva pluriorificialis, ocular-mucous membrane syndrome). Several excellent discussions of the similarities among these syndromes^{2, 4, 6, 7, 8} have been published. Most observers now believe all to have a mutual identity. The various aspects of the clinical picture have been well described—the involvement of the skin, mucous membranes of the oral cavity, conjunctivae, genital organs and other less frequently involved sites. The course is generally self-limited, and rarely is the disease fatal. Sometimes it recurs.

Two patients were diagnosed as having erythema multiforme exudativum within the same week at the United States Army Hospital, Camp Polk, Louisiana. These were the only patients so diagnosed at that hospital during at least a year and a half. Both were treated with corticotropin (ACTH), 25 mg. daily in a slow intravenous drip of 5 per cent glucose in distilled water.

REPORT OF CASES

CASE 1. The patient, a 23-year-old married Caucasian male was admitted to the hospital February 20, 1953. He had had a runny nose, cough and fever for two days. On the day of admission he had chills and higher fever than on the previous day.

Upon examination at the time of admittance the oral temperature was 103° F. Also noted were nasal congestion, redness in the throat and coarse wheezes

over both lung fields. The initial diagnosis was influenza (this was during an epidemic of influenza). Treatment was symptomatic.

The hemoglobin content of the blood was 15.2 gm. per 100 cc. Leukocytes numbered 11,700 per cu. mm.—with 82 per cent neutrophils and 18 per cent lymphocytes. The urine was normal. No abnormality was seen in an x-ray film of the chest.

The patient continued to have fever varying from 99° to 103.6° F. daily. The cough also continued and became productive, and the patient complained of generalized aches and sore throat. On the fourth hospital day, acute conjunctivitis and stomatitis developed, with vesicular and bullous lesions on the lips, mouth, pharynx and tongue. Three days later a few dark, erythematous iris-shaped lesions developed on the right arm and the back. The patient had pain on swallowing and was able to take only liquids.

On this day the diagnosis of erythema multiforme exudativum was definitely established. Administration of corticotropin was started—25 mg. daily in an intravenous drip of 5 per cent glucose in distilled water over an eight-hour period. By the next day the patient felt better and no longer appeared "toxic." After the second day of treatment no new skin lesions appeared and the conjunctivitis and stomatitis started to improve. After five days of treatment the skin lesions had faded, and the eyes and mouth were much improved. The patient was eating a soft diet and wanted to leave the hospital. Treatment was stopped and a week later the patient was released from the hospital as recovered.

When the diagnosis was suspected in this patient, he was questioned about any similar previous episodes. He said that in December of 1947 he had had a skin rash with red circles over the legs and trunk. This was accompanied by severe conjunctivitis and ulcers in the mouth and pharynx. The illness lasted approximately three weeks. No definite diagnosis was made. The treatment consisted of injections of some type. The patient said he had lost about 15 pounds during the illness. About two months later, early in 1948, all the previous signs and symptoms recurred but the oral lesions were more severe and lasted longer. This time, the illness lasted about 25 days and the decrease in body weight was between 15 and 20 pounds. A third episode occurred in June of 1948 and was of the same duration and severity as the first attack. There was no specific diagnosis

Submitted August 29, 1955.

or any specific treatment given. Some time before the first episode the patient had received a "sulfa drug" for treatment of upper respiratory tract infection. However, he had received no sulfa drug just before or during any of the subsequent illnesses.

CASE 2. A 20-year-old single Caucasian male was admitted to the hospital on February 23, 1953. He had had a cold of gradually increasing severity for three weeks. For two days prior to admission he had had headaches, sore throat, a dry nonproductive cough, and chills and fever.

At the time of admittance the oral temperature was 101.2° F. and the pharynx hyperemic. There were no abnormal sounds in the lungs. The tentative diagnosis was pharyngitis and bronchitis.

The hemoglobin content of the blood was 13.9 gm. per 100 cc. Leukocytes numbered 8,100 per cu. mm., with 78 per cent neutrophils, 21 per cent lymphocytes and 1 per cent eosinophils. The urine was normal. No abnormalities were noted in an x-ray film of the chest. Occasional colonies of beta-hemolytic *Streptococci* grew on cultures of material from the throat.

Penicillin therapy was started upon admission and was continued for eight days. On the eighth hospital day, pronounced stomatitis, conjunctivitis, balanitis, and lesions of erythema multiforme on both arms were noted. The diagnosis was changed to erythema multiforme exudativum. Administration of corticotropin was started, 25 mg. being given daily in a slow intravenous infusion of 1,000 cc. of 5 per cent glucose in distilled water. The next day the patient was afebrile and felt much better. By the fourth day of corticotropin therapy he was able to eat, and the conjunctivitis and stomatitis were much improved. The hormone was continued for five days. Two weeks from the beginning of therapy with corticotropin the patient was essentially well and was allowed out of bed. He was discharged from the hospital four days later.

The patient was carefully questioned regarding previous similar episodes. He had had intra-oral soreness thrice previously. He recalled an episode at eight years of age but could give no details. Sores

in the mouth had occurred again when he was 15 years of age and at age 17 he had had large sores in the mouth, lesions about the eyes and the glans penis, and painful urination. The patient could not recall whether or not he had taken any drugs before or during those episodes.

DISCUSSION

It was the definite opinion of the two patients who were treated and of the attending physicians that there was a pronounced change in the course of the illness in both instances within 24 hours after the initial dose of corticotropin. Not until many more patients have been treated with this hormone can there be any conclusion as to whether or not, in the cases thus far reported, administration was merely coincidental with spontaneous remission.

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EDITORIAL

C.M.A. Centennial Session

ON MAY 2 the California Medical Association completed its Centennial Session, marking the completion of one hundred years of existence and its eighty-fifth annual meeting. By all standards this was an outstanding gathering.

Scientifically, the quality of papers was extremely high and the motion pictures, colored television and scientific exhibits set new standards of excellence. Many of the papers read at the general and section meetings will appear in CALIFORNIA MEDICINE during the coming year.

The session heard a telegram directed to President Sidney J. Shipman by President Eisenhower, complimenting the C.M.A. on a century of service to the people of California. In addition, the House of Delegates greeted Governor Goodwin J. Knight and heard his direct compliments on the quality and distribution of medical care in the state and a reiteration of his adamant opposition to any legislation for socializing medicine.

On the business side, the House of Delegates staged two long sessions and dealt with three dozen resolutions which covered fields as far apart as postgraduate training and narcotic addiction. A few of the topics considered are summarized here and a complete report on the activities of the House will appear in a later issue.

One controversial item concerned the practice of private medicine by faculty members of medical schools in facilities provided by the taxpayers. This question has been under discussion in the past and, by action of the House of Delegates, has now been handed over to the C.M.A. Council for further study and report.

Another proposal which evoked debate on the floor was the suggestion that clinics or other centers be established for the administration of narcotics, at

nominal or no cost, to known addicts; as a corollary, the penalties for illicit sale of narcotics would be sharply increased. Discussion on this topic brought forth diametrically opposed points of view and the House of Delegates wound up by referring this subject also to the Council for further investigation.

Adopted without opposition was an amendment to the C.M.A. constitution which establishes a non-profit corporation to administer the Association's benevolence program. The presence of such a corporation is expected to permit the raising of funds for this worthy endeavor without the necessity of paying out federal taxes.

Another resolution urged the adoption of strong and definite standards for advertising acceptance in county medical society bulletins. Under the terms of a series of resolutions covering hospital standards, the Joint Commission on Accreditation of Hospitals will be asked to give additional study to such matters as attendance at hospital staff meetings, attendance at tissue committee meetings, handling of postgraduate training in hospitals and other items which are now under consideration by a special committee of the American Medical Association.

A renewed effort to bring the industrial fee schedule more nearly in line with accepted fee practices was approved in another resolution which asked that new representations be made to the Industrial Accident Commission in this direction.

Coming down to the business of the C.M.A., the House adopted a budget which retains 1957 dues at \$50 per active member and provides that \$10 of that amount be earmarked for medical education. As was done last year, the House specified that 80 per cent of the contribution to medical education be allotted to the three California medical

schools which are not primarily tax-supported. The budget also carried a nominal appropriation for research into the causes of malpractice actions and suggested that additional research into public relations be undertaken.

Of prime interest in the elections was the choice of a new President-Elect, for which post the House unanimously picked Dr. Frank A. MacDonald of Sacramento. Dr. MacDonald is a former member of the C.M.A. Council and a former member of the Board of Trustees of California Physicians' Service. Thus he brings to his new post a wealth of background and experience.

Dr. James C. Doyle was reelected Speaker of the House of Delegates and Dr. J. Norman O'Neill of Los Angeles was named Vice-Speaker. For members of the Council, the House selected seven incumbents to succeed themselves. Thus Drs. Omer W. Wheeler, Robert O. Pearman, Samuel R. Sherman, Ralph C. Teall, Donald C. Harrington, Arthur A. Kirchner

and T. Eric Reynolds will serve additional three-year terms.

A new office, that of an additional delegate to the A.M.A., was filled with the election of Dr. Cyril J. Attwood of Oakland, with Dr. Arlo A. Morrison of Ventura serving as his alternate. Dr. John E. Vaughan of Bakersfield was also named as an alternate delegate to the A.M.A., to fill an open office, and Dr. Hartzell H. Ray of San Mateo was similarly elected.

For the 1957 Annual Session, the Council again selected the Ambassador Hotel, Los Angeles, as the place and the dates April 28 to May 1 as the time.

Thus the Association embarks on its second century on the heels of a meeting which drew 4,550 registrants and which was considered highly successful by all. It was obvious that both the science and the business of medicine were well represented and well nourished by this annual session.

Sidney J. Shipman—A Tribute

MEDICAL ORGANIZATIONS traditionally meet each year and, among other things, elect a titular head. In the California Medical Association this is the President-Elect.

Also in the tradition is the immediate preparation of a biography of this new officer, whose capabilities are spread before the membership as an introduction to the new chief. Thereafter the President-Elect—who in his next year becomes the President—may easily become the forgotten man, the one who holds the title while the governing bodies of the organization take over full responsibility for guiding the group's policies and activities.

Periodically, however, a man so outstanding comes along that his influence and his contribution to the advancement of the principles of medicine are felt throughout the entire profession. Sidney J. Shipman, just retired as President of the C.M.A., has proved himself to be such a man.

Sid Shipman came onto the Council of the C.M.A. in 1944 after a distinguished record in the San Francisco Medical Society and an equally outstanding career as a guiding member (and later president) of the National Tuberculosis Association. His influence on the Council was soon felt and his sage thought processes advanced him to Chairman of that body in 1949. Five years later he was chosen President-Elect and for the past two years has carried on the arduous duties of office without regard to the sacrifices involved. During this period he has traveled to all parts of the state

and has discussed with local medical leaders the local, state and national problems of medicine.

Throughout his official service in the C.M.A., Sid Shipman has consistently shown the tact, the understanding, the calm approach and the inherent honesty which have elevated him to high places in the other organizations he has served. His integrity has been apparent to all and his sound and dispassionate approach to medical problems has had an effect on others which has been both soothing and efficacious.

The California Medical Association is fortunate in having had Sidney J. Shipman as its leader. It is to be hoped that he will not become the forgotten man but that his talents may continue to be available in a consulting capacity.

Every Last Sunday Until 2011

EACH YEAR from now on, anyone wishing to know the date of the opening of the Annual Session of the California Medical Association will have to remember only this: The last Sunday in April, unless that happens to be Easter; when the last Sunday is Easter, the meeting will begin the first Sunday in May.

This rule, adopted by the Council at its most recent meeting, will make long-range planning easier not only for the C.M.A. but also for other organizations that may wish to relate the dates of their meeting to ours or to avoid conflict or overlapping.

By the way, unless something happens to throw the universe out of kilter, the next time Easter will fall on the last Sunday in April is the year 2011.

Letters to the Editor...

The following letter is a copy of one addressed primarily to American Diabetes Association, Inc., New York City.

Gentlemen:

The diabetic identification card, shown on page 21 of *Forecast* for May-June, 1956, is pretty, but for some very real purposes, is not worth the thin dime it costs to obtain. I am speaking from the standpoint of a physician of 40 years experience who, for more than that many years, has been familiar with police problems and who has, for a bit more than 4 years, been mildly diabetic.

In the first place, there are many similar diabetic identification cards in circulation none of which, including the card mentioned, can be expected to have any standing with law enforcement officers. In Los Angeles, and undoubtedly throughout the country, many "winos" and other chronic alcoholics who are *not* diabetic carry such diabetic identification cards and use them to try to talk the officer out of arresting them. For this reason, I know of no place where such cards are given consideration by police. The police cannot take to a physician every drunk who waves a diabetic identification card at them.

We cannot reasonably expect this situation to be improved as long as such cards are so easily obtained. To broadcast these cards in this manner reduces them to about the same value as a lead nickel. If perfect copies of the badges worn by the police of New York City were as easily obtainable as diabetic identification cards, no one would be able to distinguish between the real and the false and a person flashing a New York Police badge would have less authority than a Hottentot waving a spear.

Several years ago I wrote to Dr. Joslin and proposed the following system of diabetic identification cards. Dr. Joslin replied that he thought the idea

was excellent and that he was referring my letter to the A.D.A. It was evidently ignored.

1. Have some nationwide organization, such as the A.M.A. and its component societies, handle registration of diabetics and issue registered diabetic identification cards.

2. Have one standard registered diabetic identification card, *all* such cards to be *serially numbered* and, preferably, to carry a small photograph of the person to whom issued.

3. Have these cards issued *only* by centrally located units, such as the County or State Medical Societies, which shall keep a register by names and serial numbers of the cards and the persons to whom issued.

4. Provide standardized application forms to be filled out by the diabetic's personal physician, certifying to the fact that the person is diabetic, and requesting that a registered diabetic identification card be issued.

5. Registered diabetic cards to be issued *only* on the basis of certification as outlined above.

6. For purposes of permanency have diabetic identification cards mounted between plastic.

7. Establish a fee for such cards to cover cost of the cards and administration of the program, with provisions for free issuance to indigents.

Only by such a program can a diabetic identification card be expected to be respected by law enforcement personnel. Until such a program is established *do not* blame the police for the diabetic who erroneously lands in the drunk tank instead of the hospital.

Very truly yours,
JOHN H. SCHAEFER, M.D.

525 South Flower Street
Los Angeles

California MEDICAL ASSOCIATION

NOTICES & REPORTS



Frank A. MacDonald, M.D.

ON MAY 2, the C.M.A. House of Delegates unanimously elected Frank A. MacDonald of Sacramento to the post of President-Elect.

Dr. MacDonald was born in Rhode Island, of good Scotch parents. He went to school in Vermont till the age of 19, when good judgment prevailed and he persuaded his family to move to California. He did college work at the University of Southern California and then at Stanford, taking an A.B. degree at Stanford in 1921. He continued in the Stanford Medical School till he received his M.D. in 1925. After postgraduate work in surgery, he

entered the private practice of surgery in Sacramento in 1928 and is still so engaged.

Dr. MacDonald has been a member of the visiting staff of Sutter and Mercy Hospitals since 1928 and served as president of the staff of Mercy Hospital in 1953.

He was a member of the board of directors of the first hospital insurance plan in the United States (a pioneer blue cross plan) from 1932 to 1936. He was president of the Sacramento Society for Medical Improvement in 1936 and a delegate from that society to the C.M.A. in 1937 and 1938. In 1939 he succeeded Junius B. Harris as councilor from the eighth district (now the eleventh) and served as councilor for three terms, from 1939 to 1948. In 1949 he became a trustee of California Physicians' Service where he served two terms, to 1955. Of this time three years were spent on the C.P.S. fee schedule committee. He served on the C.M.A. committee on postgraduate activities from 1943 to 1944, on the legislative advisory committee from 1948 to 1954 and on the committee on Public Relations from 1951 to 1954. He served as a member of the Industrial Accident fee schedule committee for two terms.

In 1949 Dr. MacDonald became an alternate delegate from the C.M.A. to the A.M.A. and in 1952 was advanced to delegate, a position which he now holds.

DONALD A. CHARNOCK, M.D.	President
FRANK A. MacDONALD, M.D.	President-Elect
JAMES C. DOYLE, M.D.	Speaker
J. NORMAN O'NEILL, M.D.	Vice-Speaker
DONALD D. LUM, M.D.	Council Chairman
ALBERT C. DANIELS, M.D.	Secretary-Treasurer
IVAN C. HERON, M.D.	Chairman, Executive Committee
DWIGHT L. WILBUR, M.D.	Editor
JOHN HUNTON	Executive Secretary
General Office, 450 Sutter Street, San Francisco 8	
ED CLANCY	Director of Public Relations

Southern California Office:
417 South Hill Street, Los Angeles 13 • Phone MAdison 6-0683

He has been a fellow of the American College of Surgeons (of which he is a life member) since 1934, and he served as president of the Northern California Chapter of the college in 1954.

Dr. MacDonald has a charming wife, Caroline, who often accompanies him to medical meetings. He has one son who is at present serving as assistant resident in surgery at Baylor University Medical School in Houston.

Dr. MacDonald is an ardent advocate of the value of medical organization and a staunch supporter of the C.M.A. and the A.M.A. He holds deep and firm convictions on a great variety of medical, political and socioeconomic problems and is vigorous in advancing and supporting these convictions. This vigor is tempered by an abiding sense of responsibility and is guided by one paramount principle, "Is the proposed course good for all of medicine and for all the people?" And firm though his convictions may be, he has the courage and the stature to change his position when this is shown to be desirable by changes in perspective and by development of events.

Conscientious, hard working, serious in approaching problems assigned to him, thorough and thoughtful in developing solutions to them, he attacks all his problems with a youthful zest that is contagious, and that offers a continuing challenge to his conferees of whatever age.

Through the years he has made a host of friends in the state government, from the janitor to the governor, and has given freely of his professional skill to so many members of the government that his friend, Dr. Dwight Murray, often refers to him as the "surgeon general of the legislature."

The office he now holds is regarded by many as an honor to be given in reward for past service. Frank MacDonald richly deserves this honor for the many years of devoted service he has given to the C.M.A.; and California physicians are eager and happy to honor him in this way. Of far greater importance is the honor he does to his colleagues in accepting this new responsibility and in sacrificing his personal and professional life for unselfish service to the profession which he loves.

RALPH C. TEALL, M.D.

Council Meeting Minutes

Tentative Draft: Minutes of the 417th Meeting of the Council of the California Medical Association, San Francisco, St. Francis Hotel, March 24, 1956.

The meeting was called to order by Chairman Lum in Room 220 of the St. Francis Hotel, San Francisco, at 9:30 a.m., Saturday, March 24, 1956.

Roll Call:

Present were President Shipman, President-Elect Charnock, Speaker Doyle, Secretary Daniels, Editor Wilbur and Councilors West, Wheeler, Loos, Wadsworth, Harrington, McPharlin, Lum, Bostick, Reynolds, Varden, Heron, Carey and Rosenow.

A quorum present and acting.

Absent for cause, Vice-Speaker Foster, Councilors Pearman, Teall and Kirchner.

Present by invitation, Messrs. Hunton, Clancy, Thomas and Gillette of C.M.A. staff; Howard Hassard, legal counsel; Drs. Carl M. Hadley and Arlo A. Morrison; Fred O. Field, legal counsel to the Los Angeles County Medical Association; and county society executive secretaries Bannister of Orange, Marvin of Riverside, Foster of Sacramento, Nute of San Diego, Neick of San Francisco, Thompson of San Joaquin, Wood of San Mateo, Donovan of Santa Clara, DeVere of Stanislaus and Funk of Solano.

1. Minutes for Approval:

(a) On motion duly made and seconded, minutes of the 416th meeting of the Council, held February 12, 1956, were approved.

(b) On motion duly made and seconded, minutes of the 256th meeting of the Executive Committee, held March 17, 1956, were approved.

2. Membership:

(a) A report of membership as of March 23, 1956, was received and ordered filed.

(b) On motion duly made and seconded in each instance, 15 applicants were voted Retired Membership. There were: Edwin W. Merrithew, Charles C. Morison, Clifford D. Sweet, Alameda-Contra Costa County; Charles R. Gailmard, Antony J. Greco, Los Angeles County; Cyril E. Lewis, Placer-Nevada-Sierra County; Ward C. Alden, K. L. Dole, James S. Forsythe, David C. Mock, San Bernardino County; Ethel D. Owen, San Francisco County; Gifford Sobey, San Luis Obispo County; Dorothea Lee, Charlotte L. Marvin, Charles E. Moore, Santa Clara County.

(c) On motion duly made and seconded in each instance, 22 applicants were voted Associate Membership. These were: Max W. Biggs, P. H. Calkins, Leslie Corsa, Jr., Francis A. Munson, Richard N. Reedy, Alameda-Contra Costa County; Gerald Fin-

kel, Dean W. Gilman, A. E. Hirst, Jr., Wilfred M. G. Jones, Howard A. Joos, William E. Nerlich, Los Angeles County; Bessie C. Martell, Napa County; John D. Reese, A. E. T. Rogers, Fletcher C. Stewart, Orange County; Laurens P. White, S. K. Hockstetler, Gilbert M. Loewe, San Francisco County; Thelma M. Quinn, Raymond H. Somers, Santa Clara County; Arthur J. Nash, Solano County; Elmo Alexander, Tulare County.

(d) On motion duly made and seconded in each instance, reductions of dues were voted for 16 applicants for reasons of illness or postgraduate study.

3. *Student American Medical Association:*

(a) On motion duly made and seconded, it was voted to meet the expenses of one representative of the California chapters of the Student A.M.A. in attending the inaugural meeting in New York to announce Medical Education Week.

(b) On motion duly made and seconded, it was voted to permit the California Chapters of the Student A.M.A. to send two representatives to the annual meeting of that organization, with the Association meeting tourist transportation costs for such representatives.

4. *Committee on Public Health and Public Agencies:*

Councilor West reported that the Advisory Committee to the Crippled Children's Services was continuing its study of the criteria to be used in qualifying specialists to handle cases in this field.

5. *Woman's Auxiliary:*

On motion duly made and seconded, it was voted to commend the Woman's Auxiliary for its generous contributions to the families of physicians who had suffered damages in the recent floods.

On motion duly made and seconded, it was voted to appoint Drs. R. Stanley Kneeshaw and Robert M. Shelton as members of the Advisory Committee to the Woman's Auxiliary for the 1956-1957 year.

6. *Nominations for C.P.S. Trustees:*

Councilor Sherman reported that his committee had voted to nominate Drs. Leon O. Desimone, Mer-

lin L. Newkirk, Robb Smith and Bert L. Halter and Mr. Robert A. Hornby for election as Trustees of California Physicians' Service. On motion duly made and seconded, these nominations were approved.

Adjournment:

There being no further business to come before it, the meeting was adjourned at 4:45 p.m.

DONALD D. LUM, M.D., *Chairman*
ALBERT C. DANIELS, M.D., *Secretary*

Executive Committee Minutes

Tentative Draft: Minutes of the 257th Meeting of the Executive Committee of the California Medical Association, San Francisco, March 24, 1956.

The meeting was called to order by Chairman Heron in Room 220 of the St. Francis Hotel, San Francisco, on Saturday, March 24, 1956, at 12:30 p.m.

Roll Call:

Present were President Shipman, President-Elect Charnock, Speaker Doyle, Council Chairman Lum, Auditing Committee Chairman Heron, and, ex-officio, Secretary Daniels.

Present by invitation were Councilor Hollis L. Carey, Messrs. Hunton, Clancy, Gillette and Thomas of C.M.A. staff, and legal counsel Hassard.

A quorum present and acting.

1. *Loans to Flood Victims:*

The committee reviewed applications from nine members for loans from funds voted earlier by the Council, for the rehabilitation of damages caused by floods in several counties. On motion duly made and seconded, several such loans were approved for immediate disbursement.

Adjournment:

There being no further business to come before it, the meeting was adjourned at 12:40 p.m.

IVAN C. HERON, M.D., *Chairman*
ALBERT C. DANIELS, M.D., *Secretary*

In Memoriam

BODMAN, EDWARD W. Died in San Marino, April 20, 1956, aged 76. Graduate of Rush Medical College, Chicago, 1907. Licensed in California in 1927. Doctor Bodman was a member of the Los Angeles County Medical Association.



BROWN, GEORGE W. Died March 29, 1956, aged 73. Graduate of Central Medical College of St. Joseph, Missouri, 1898. Licensed in California in 1913. Doctor Brown was a retired member of the Los Angeles County Medical Association, the California Medical Association, and an associate member of the American Medical Association.



CAMPICHE, PAUL S. Died in Lausanne, Switzerland, April 22, 1956, aged 80. Graduate of the Université de Lausanne Faculté de Médecine, Switzerland, 1899. Licensed in California in 1908. Doctor Campiche was a retired member of the San Francisco Medical Society, the California Medical Association, and an associate member of the American Medical Association.



CHAIN, JOHN N. Died in Eureka, April 14, 1956, aged 79. Graduate of the University of California Medical School, Berkeley-San Francisco, 1904. Licensed in California in 1904. Doctor Chain was a member of the Humboldt County Medical Society, a life member of the California Medical Association, and an associate member of the American Medical Association.



COPELAND, EDWIN KING. Died in Woodland, April 18, 1956, aged 56. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1930. Licensed in California in 1936. Doctor Copeland was a member of the Yolo County Medical Society.



FUIKS, DELLIVAN M. Died in Sacramento, April 17, 1956, aged 52. Graduate of the State University of Iowa College of Medicine, Iowa City, 1927. Licensed in California in 1938. Doctor Fuiks was a member of the Sacramento Society for Medical Improvement.



HAUMEDER, HANS. Died in Oakland, April 27, 1956, aged 65, of heart disease. Graduate of the Medizinische Fakultät der Universität, Wien, Austria, 1914. Licensed in California in 1943. Doctor Haumeder was a member of the Alameda-Contra Costa Medical Association.



LEE, LINFORD H. Died in Los Angeles, April 11, 1956, aged 62, of heart disease. Graduate of the University of Nebraska College of Medicine, Omaha, 1921. Licensed in California in 1928. Doctor Lee was a member of the Los Angeles County Medical Association.

MANNING, ARMAS A. Died in Los Angeles, April 24, 1956, aged 49. Graduate of Wayne University College of Medicine, Detroit, Michigan, 1935. Licensed in California in 1935. Doctor Manning was a member of the Los Angeles County Medical Association.



MCLEAR, LOWELL E. Died in Berkeley, April 15, 1956, aged 46, of subdural hematoma due to trauma. Graduate of the University of Oregon Medical School, Portland, 1935. Licensed in California, 1937. Doctor McAlear was a member of the Alameda-Contra Costa Medical Association.



PRATT, MATHEW D. Died recently. Graduate of the University of California Medical School, Berkeley-San Francisco, 1900. Licensed in California in 1901. Doctor Pratt was a member of the Shasta County Medical Society, a life member of the California Medical Association, and an associate member of the American Medical Association.



STEINBERG, JAMES. Died in Los Angeles, April 23, 1956, aged 66, of heart disease. Graduate of Cornell University Medical College, New York, 1911. Licensed in California in 1911. Doctor Steinberg was a member of the Los Angeles County Medical Association.



WILSON, DOXEY R. Died in San Jose, May 1, 1956, aged 72, from a fall in his home. Graduate of Cooper Medical College, San Francisco, 1908. Licensed in California in 1908. Doctor Wilson was a member of the Santa Clara County Medical Society.



WINTERS, WALTER PAYNE. Died in San Diego, November 9, 1955, aged 85, of a cerebral vascular accident and arteriosclerosis. Graduate of the New York Medical College, Flower and Fifth Avenue Hospitals, New York, 1906. Licensed in California in 1910. Doctor Winters was a retired member of the San Diego County Medical Society, the California Medical Association, and an associate member of the American Medical Association.



WOOD, DENNISTOUN, JR. Died April 11, 1956, aged 50. Graduate of Stanford University School of Medicine, Stanford University-San Francisco, 1938. Licensed in California in 1938. Doctor Wood was a member of the Santa Clara County Medical Society.



WOOD, GRANVILLE NEWMAN, JR. Died in Palo Alto, May 2, 1956, aged 67, of heart disease. Graduate of Stanford University School of Medicine, Stanford University-San Francisco, 1924. Licensed in California in 1924. Doctor Wood was a member of the Santa Clara County Medical Society.



WOMAN'S AUXILIARY

TO THE CALIFORNIA MEDICAL ASSOCIATION

A Summing Up

During the past year, your Woman's Auxiliary has seen growth in both size and activity. At this writing, our membership has topped 6,440, and with new members coming in daily we expect to pass the 6,500 mark before our year's record is in.

These thousands of Auxiliary members have not been idle. Due to their hard work and good ideas, the California Woman's Auxiliary leads the United States not only in size but in its large and productive program.

Organized Activities

Some of the work which your Auxiliary has done in the past year can be measured in dollars and cents. For instance:

For **American Medical Education Foundation**, we have raised \$6,910 to date, with two counties yet to report. This is well above our \$1-a-member goal, and already some \$1,100 above the sum raised the previous year.

For **Physicians' Benevolence**, we have raised over \$3,500—also incomplete returns. While this is not up to the mark we had set, it is well above amounts previously raised.

For **Nurse Recruitment**, your Auxiliary has accounted for the sums of \$25,500 for Scholarships and \$5,000 in loans . . . plus \$400 used for materials and \$50 for other expenses of our program. This brings the grand total—and it is grand—to \$30,950.

For **Community Service Groups** such as Red Cross, Blood Banks, Cerebral Palsy Programs, etc.; for **Hospitals**; for **Christmas Donations**; your Auxiliary has raised a total of more than \$16,000 in the past year.

Of equal importance is some of the less tangible work that we have done. Twenty-three counties have had programs in **Mental Health**, with much time being spent with geriatric patients and in rehabilitation. A significant contribution has also been made in this field in helping to change the public attitude toward mental disease.

In **Legislation**, your Auxiliary has continued to work actively with the C.M.A. and to support its legislative program . . . in **Civil Defense**, we have continued to participate in our community programs . . . in promoting *Today's Health*, at least six of our counties have topped their subscription quota, and we are over 1,000 subscriptions ahead of our previous record.

Courier Remains Tops

The official publication of your Woman's Auxiliary, *Courier* was last year once again recognized officially as the best of its kind in the coun-

try. Its importance is being recognized locally, too, by the upping of its yearly budget to \$5,000, and by specifying that it is to have at least five issues yearly, with the dates of publication now defined in our by-laws.

Revision of By-Laws

As our organization has grown, so have the problems of our administration. Last year saw some needed changes made in our by-laws. Among the more noteworthy of these changes was the addition of a Spring Board Meeting, and the streamlining of our State Board of officials.

Budget Changes

Our new budget also reflects our growth. New provisions now allow for two delegates to attend the National Convention, both president and president-elect. More newsworthy, perhaps, is the fact that the new budget at last makes allowance for the rise in the cost of travel, and these ladies can now go "first class."

Flood Assistance

Your Auxiliary gratefully acknowledges the commendation received from the C.M.A. Council for our work in assisting physicians' families who were victims of the tragic floods last December. We are proud that we were able to raise \$5,000 for their use "with no strings attached." Of this amount, \$500 was contributed by the National Auxiliary, \$1,000 by the State Auxiliary, and the rest by County Auxiliaries and by personal donations from Auxiliary members.

Incidentally, some of our work in civil defense paid off well during the flood disaster period. Auxiliary members who were familiar with civil defense procedures were able to work well with the authorities during the disaster period. And members familiar with the nurses' aide courses or practical nurses' courses found that their knowledge stood them in good stead.

Ave Atque Vale

It has been our privilege and pleasure to work for and with the C.M.A. during the past year. To all of you who have given us guidance, counsel and encouragement, we express our deep and sincere thanks. We hope that we can take some pride in our year's achievements—and, more important, we hope that you can, too.

NEWS & NOTES

NATIONAL • STATE • COUNTY

ALAMEDA

Dr. Paul C. Samson, Oakland, was installed as president of the American Trudeau Society at the annual meeting of the National Tuberculosis Association, held last month in New York City. Dr. Samson is a past president of the California Tuberculosis and Health Association.

FRESNO

Dr. Kendall B. Holmes was elected president of the Fresno County Heart Association at a recent meeting of the association. He succeeds Dr. Leopold J. Snyder. Dr. J. Malcolm Masten was elected vice-president and Dr. Bruce Berg, secretary.

LOS ANGELES

Beginning July 13, 1956, the Postgraduate Division of the School of Medicine of the University of Southern California will commence a **year-long home course in electrocardiography**. Each week a particular subject will be discussed and exemplified by accompanying tracings. In addition "unknown" electrocardiograms on subjects already discussed will be included. The following week a detailed interpretation of the "unknown" tracings will be attached to the new lesson. The fee is \$100 for 52 weeks. Further information may be obtained from Phil R. Manning, M.D., director, Postgraduate Division, USC School of Medicine, 2025 Zonal Avenue, Los Angeles 33.

* * *

At the annual meeting of the Los Angeles County Heart Association last month, **Dr. Edward Shapiro**, Beverly Hills, was elected president to succeed Dr. Alex A. Roger, also of Beverly Hills. Dr. Mitchell D. Covel was elected vice-president and Dr. Sidney S. Sobin, secretary.

* * *

Dr. Joseph L. Robinson of Los Angeles was elected president of the California Tuberculosis and Health Association at the annual meeting held in San Francisco in April.

* * *

The University of California Extension will join with the UCLA School of Medicine to give a **summer 1956 course in Techniques of Hypnosis**. The three-day course will meet in the first floor lecture room of the Medical Center on the Los Angeles Campus July 9, 10, and 11, with the program consisting of demonstrations and practice training. It is designed to acquaint physicians and dentists with methods of inducing hypnosis, the techniques of inducing various degrees of hypnosis in various types of patients, and the control of patients with different kinds of problems. Fee for the course is \$50.

A course in Advanced Techniques and Application of Hypnosis meets at the Los Angeles Medical Center July 11, 12, and 13. Fee for this course is \$100.

Registration blanks and information sheets concerning both courses are available on request to University of California Extension, Medical, Los Angeles 24 (BRadshaw 2-6161).

Some 120 medical golfers participated in the California Medical Association **golf tournament** which was played at the Wilshire Country Club, Los Angeles, at the time of the C.M.A. annual meeting. Dr. Al Heldfond, a 16 handicapper from Beverly Hills, made the course in 78 strokes for a net 62. He won the Boyle & Co. perpetual low net trophy for this state tournament. Dr. Paul Travis of Downey had the low gross with a 72.

Following is a list of other winners in the various classifications:

CLASS A

Classification	Name	Net Score
First low net	K. Kearns	68
Second low net	S. Azen	69
Third low net	J. Moore	69
Fourth low net	G. Erickson	70
First low gross	W. Williams	76
Second low gross	J. Albers	77

CLASS B

First low net	H. Zide	66
Second low net	A. Ollstein	68
Third low net	G. B. Smith	70
Fourth low net	N. Schumaker	70
First low gross	U. Wissner	82
Second low gross	E. Crane	86

CLASS C

First low net	R. McKenna	66
Second low net	J. Frieden	67
Third low net	J. R. Johnson	69
Fourth low net	A. Hedge	71
First low gross	H. Briskin	95
Second low gross	R. Burnett	96

SAN DIEGO

Dr. Homer D. Peabody, Jr., was installed as president of the San Diego County Tuberculosis and Health Association at a recent meeting of the organization, and **Dr. Albert L. Anderson** was elected president-elect. Dr. Peabody succeeded Dr. David H. Thompson.

SAN FRANCISCO

Dr. William C. Voorsanger, San Francisco, was presented with an award and certificate for "outstanding accomplishment and service in the field of chest diseases in California and nationally" at the annual meeting of the California Chapter of the American College of Chest Physicians, which was held in Los Angeles last April.

* * *

Dr. Gerald B. O'Connor, San Francisco, was elected president of the California Society of Plastic Surgeons at the annual meeting of the society, held recently at Del Monte.

* * *

A grant from the Muscular Dystrophy Association, Inc., has made it possible to expand services at Children's Hospital for **patients with muscular dystrophy and amyotonia**, according to an announcement from the hospital. Services available (not limited to residents of San Francisco) are: Physical therapy, occupational therapy and social service—all under medical supervision.

Referral is by private physician or clinic. The referral should be accompanied by a summary of diagnostic studies.

Admissions are made through the Muscular Dystrophy Clinic conducted the third Wednesday of each month under the supervision of Drs. Lloyd E. Hardgrave and Robert Terry.

Appointments may be made by calling Children's Hospital, Bayview 1-1200, and asking the operator for Physical Therapy, extension 387.

Information may be obtained by phoning or writing to Mrs. Miriam Peizer, Social Worker, Children's Hospital, 3700 California Street, San Francisco.

Among the unrestricted grants of \$4,850,000 to seven university medical schools announced recently by the Commonwealth Fund was one of **\$1,000,000 to Stanford University School of Medicine**. The awards may be used in whatever ways the schools consider most effective to improve their programs of medical education. There is a proviso, however, that the school must raise funds to match the amount of the grant.

"In making these grants," the announcement said, "the Fund recognizes the urgent and increasing need for funds for strengthening faculty and raising teaching salaries, clarifying educational objectives, reviewing curricula and restructuring programs of medical education. However, since each medical school's specific requirements differ in priority, the Fund places no restrictions on these gifts."

GENERAL

Representatives of state societies of internal medicine met in Los Angeles in April, just before the annual meeting of the American College of Physicians and completed arrangements for the **formation of the American Society of Internal Medicine** to coordinate and strengthen the activities of the various state societies of internal medicine at a national level. Officers and committee members who will serve as an interim committee include Dr. Lewis T. Bullock,

Los Angeles, chairman; and Dr. Claude P. Callaway, San Francisco, secretary-treasurer. National headquarters of the newly formed organization for the current year will be at San Francisco, present headquarters of the California Society of Internal Medicine.

* * *

Twenty-eight Californians were **elected to fellowship in the American College of Physicians** at the annual meeting of the organization which was held in Los Angeles last April. They are: Olov Albert Blomquist, Los Angeles; Ralph Bookman, Los Angeles; Robert Irving Boyd, Pasadena; Robert Rayner Commons, Beverly Hills; Eliot Corday, Beverly Hills; James Newton DeLamater, San Marino; Sim Pope Dimitroff, Hollywood; Edmund Lawrence Dubois, Beverly Hills; Archie Lee Edgar, San Diego; Hugh Allen Edmondson, Los Angeles; Benjamin B. Faguet, San Diego; John Walker Findley, Jr., San Mateo; James Thomas Fowler, Jr., Long Beach; Frederick Mullen Hebert, Berkeley; William Lane Hewitt, Los Angeles; Ralph E. Homann, Jr., Los Angeles; Bernard Hyde, Los Angeles; William Frederick Luttgens, San Francisco; William Earl McCullough, Santa Barbara; Lee Munroe, San Diego; Robert William Oblath, North Hollywood; William Francis Oliver, Santa Barbara; John Lucien Reynolds, Los Angeles; Michael A. Rubinstein, Beverly Hills; Ernest W. Shaw, San Diego; Norman Wesley Specht, Los Angeles; Jerome Victor Treusch, Beverly Hills; and Arthur Edward Varden, San Bernardino.

POSTGRADUATE EDUCATION NOTICES

THIS BULLETIN of the dates of postgraduate education assemblies and the meetings of various medical organizations in California is supplied by the Committee on Postgraduate Activities of the California Medical Association. In order that they may be listed here, please send communications relating to your future medical or surgical programs to: Mrs. Margaret H. Griffith, Assistant Director, Postgraduate Activities, California Medical Association, 417 South Hill Street, Los Angeles 13.

UNIVERSITY OF CALIFORNIA AT LOS ANGELES

Dermatology, 1956, June 22 and 23. Ten and one-half hours. Fee: \$35.00.

Laboratory Technicians Symposium, June 23 and 24. Twelve hours. Fee: \$20.00.

Techniques of Hypnosis, July 9 to 11. Fifteen hours. Fee: \$50.00.

Advanced Techniques and Application of Hypnosis, July 11 to 13. Fifteen hours. Fee: \$100.00.

Recent Advances in Surgery, July 16 to 18. Nineteen and one-half hours. Fee: \$50.00 for three days, \$20.00 per day.

Surgery of Trauma, July 19 and 20. Twelve hours. Fee: \$35.00.

Recent Advances in Medicine, July 23 to 27. Thirty-five hours. Fee: \$75.00 for full week or \$20.00 per day.

Anesthesia Seminar, August 27 to 29. Eighteen hours. Fee: \$50.00.

Contact: Thomas H. Sternberg, M.D., Assistant Dean for Postgraduate Medical Education, U.C.L.A., Los Angeles 24. BRadshaw 2-8911, Ext. 202.

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Fundamental Principles of Radioactivity and the Diagnostic and Therapeutic Uses of Radioisotopes. Two or three month course limited to one enrollee per month. Tuition: \$250.00 per month.

Internal Medicine at the Bedside, June 18-22. Forty hours. Fee: \$100.00.

Contact: Seymour M. Farber, M.D., Head, Postgraduate Instruction, Office of Medical Extension, University of California Medical Center, San Francisco 22. MOntrose 4-3600, Ext. 665.

UNIVERSITY OF SOUTHERN CALIFORNIA, LOS ANGELES

Diagnosis and Management of Cardiovascular Diseases, July 20, 21 and 22, Hotel Statler and Good Hope Clinic, twenty-four hours. Fee: \$65.00. Registration closes July 10, 1956.

Home Course in Electrocardiography. Begins July 13. Fifty-two weeks. Fee: \$100.00.

Cardiac Resuscitation. Sponsored by the Los Angeles County Heart Association each Wednesday throughout the year, 4 to 6 p.m. Residents admitted without fee. Tuition for all other physicians: \$30.00. (Each session all-inclusive.)

Contact: Phil R. Manning M.D., Director of Medical Extension Education, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 33. CApital 5-1511.

COLLEGE OF MEDICAL EVANGELISTS

Anesthesiology. Daily, full-time, four months, beginning each four months. Fee: \$300.

Diseases and Injuries of Bones and Joints. Daily, July 2 to July 31. Full time. Fee: \$100.00.

Basic Science Course in Surgery. Full time, nine months beginning October 1. Fee: \$800.00.

Contact: Chairman, Section on Graduate and Postgraduate Medicine, College of Medical, Evangelists, 1720 Brooklyn Ave., Los Angeles 33. Angelus 9-9131, Ext. 205.

CALIFORNIA MEDICAL ASSOCIATION POSTGRADUATE INSTITUTE

SACRAMENTO VALLEY COUNTIES in association with Stanford University School of Medicine, June 21, 22, 23, Cal-Neva Lodge, Lake Tahoe.

Contact: C. A. Broadus, M.D., Director of Postgraduate Activities, P.O. Box A-1, Carmel, California, or Mrs. Margaret H. Griffith, Assistant Director, Postgraduate Activities, California Medical Association, 417 So. Hill St., Los Angeles 13.

Medical Dates Bulletin

SUMMER MEETINGS

IDAHO STATE MEDICAL ASSOCIATION annual meeting, June 17-20, Sun Valley, Idaho.

Contact: Armand L. Bird, executive secretary, Idaho State Medical Association, 364 Sonna Building, Boise, Idaho.

MEDICAL LIBRARY ASSOCIATION 55th annual meeting, June 18 to 22, Hotel Statler, Los Angeles.

Contact: Mrs. Ella Crandall, librarian, Los Angeles County General Hospital, Los Angeles.

WYOMING STATE MEDICAL SOCIETY annual meeting, Jackson Lake Lodge, Moran, Wyoming, June 29 and 30.

Contact: A. R. Abbey, Box 2036, Cheyenne, Wyoming.

COLORADO DIVISION OF THE AMERICAN CANCER SOCIETY 10th annual Rocky Mountain Cancer Conference, Shirley-Savoy Hotel, Denver, Colorado, July 11 and 12.

Contact: John S. Bouslog, M.D., 835 Republic Building, Denver 2, Colorado.

NEVADA STATE MEDICAL ASSOCIATION annual meeting in conjunction with Reno Surgical Society, Riverside Hotel, Reno, Nevada, August 22 to 25.

Contact: Lowell Peterson, M.D., chairman, Arrangements and Program Committee, 130 North Virginia St., Reno, Nevada.

SEPTEMBER MEETINGS

ST. JOHN'S HOSPITAL Postgraduate Assembly, September 10, 11, 12, 9 a.m. to 4 p.m. and 8 to 9 p.m. Elks Club, Santa Monica.

Contact: John C. Eagan, M.D., Director, 1245 Glendon Ave., Los Angeles 24.

STOCKTON POSTGRADUATE STUDY CLUB, Thursday evenings, September 13 to November 15, Stockton State Hospital.
Contact: A. Merchant, M.D., Medical-Dental Bldg., Stockton.

WASHINGTON STATE MEDICAL ASSOCIATION Annual Meeting, Olympic Hotel, Seattle, September 16-19.

Contact: Mr. Ralph W. Neill, executive secretary, 1309 Seventh Ave., Seattle, Washington.

SAN DIEGO COUNTY GENERAL HOSPITAL TENTH ANNUAL POSTGRADUATE ASSEMBLY. September 19-20.

Contact: Howard B. Kirtland, Sr., M.D., Chairman, Postgraduate Committee, 3505 Fourth Avenue, San Diego 3.

CALIFORNIA SOCIETY OF INTERNAL MEDICINE ANNUAL MEETING. September 29, La Playa Hotel, Carmel.

Contact: Mrs. Mildred B. Coleman, Assistant Secretary, Room 515, 384 Post Street, San Francisco 8.

OCTOBER MEETINGS

SAN FRANCISCO HEART ASSOCIATION Annual Postgraduate Symposium, October 3, 4, 5, 1956, St. Francis Hotel, San Francisco.

Contact: Executive director, 604 Mission St., San Francisco.

ALAMEDA-CONTRA COSTA DIABETES ASSOCIATION one-day Symposium on Oral "Insulinoids," October 3, Highland-Alameda County Hospital, Oakland.

Contact: Institute for Metabolic Research, Highland-Alameda County Hospital, Oakland.

AMERICAN CANCER SOCIETY, California Division, Annual Cancer Conference, October 4, 2 to 5 p.m., Fairmont Hotel, San Francisco.

Contact: Otto Pflueger, M.D., Conference chairman, 384 Post St., San Francisco.

HERRICK MEMORIAL HOSPITAL Medical Staff Second Annual Postgraduate Symposium, 9 a.m.-5 p.m., October 5, Berkeley High School Little Theatre, Allston Way between Grove and Milvia, Berkeley, Calif.

Contact: Administrator's Office, Herrick Hospital, Berkeley, or telephone: THornwall 5-0130.

SAN DIEGO COUNTY HEART ASSOCIATION Professional Symposium, U. S. Naval Hospital Auditorium, Balboa Park, San Diego, October 9.

Contact: O. Martin Avison, executive director, San Diego County Heart Association, 1651 Fourth St., San Diego 1.

LOS ANGELES COUNTY HEART ASSOCIATION 26th Annual Symposium on Heart Disease, Wilshire-Ebell Theatre, 4401 West 8th St., Los Angeles, October 10 and 11.

Contact: Robert A. Pike, executive director, Los Angeles County Heart Association, 316 South Bonnie Brae, Los Angeles 57 or telephone DUnkirk 8-4127.

CALIFORNIA ACADEMY OF GENERAL PRACTICE 8th Annual Scientific Assembly, Hotel Statler, Los Angeles, October 14, 15, 16, 17.

Contact: William W. Rogers, executive secretary, California Academy of General Practice, 461 Market St., San Francisco.

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KEY TO ABBREVIATIONS USED

(Or.)—Original Article; (Ed.)—Editorial; (CMA)—California Medical Association; (CR)—Case Report; (I)—Information; (IE)—Letters to the Editor; (MJ)—Medical Jurisprudence.

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